CardioTeam Spotlight Session

Prevention Clinics Improve Outcomes for Cardiovascular Disease Patients

Recognizing the growing importance of prevention efforts in stemming the tide of cardiovascular disease, the CardioTeam Spotlight Session yesterday morning focused on the team aspects of the services provided in prevention clinics, including the clinical aspects of treating patients in prevention clinics and adherence issues in preventive care.

The best outcomes for patients who receive preventive care result from the efforts of a team composed of cardiologists and other health care providers, including nurses, nurse practitioners, physician assistants, dieticians, and clinical pharmacists, said H. Robert Superko, MD, director of the Center for Prevention at the American Cardiovascular Research Institute and director of the Cholesterol, Genetics and Heart Disease Institute, Burlingame, Calif.

"Who does a better job of getting patients to lower their lipid levels, cardiologists or nurses?" Dr. Superko asked the audience. The answer, as demonstrated in the 1988 Multifit Trial, is that nurses are better at helping patients adopting lifestyle patterns that help lower lipid levels, such as consuming healthier diets, exercising, and taking their medications.

In 1990, Kaiser Permanente of Northern California began using a prevention clinic model studied in the Multifit Trial and was able to decrease mortality rates from cardiovascular disease in its patients by 15 percent, so that CVD was no longer the leading cause of death in this population. The average length of hospital stay was also reduced. "The team approach made the difference," Dr. Superko said.

Brenda C. Garrett, RN, from the American Cardiovascular Research Institute in Atlanta, Ga., reviewed a number of case studies of patients treated in prevention clinics, showing that care provided by a cardioteam helps prevent and reduce cardiovascular events.

Prevention clinics are effective in identifying patients' risk factors for cardiovascular disease, teaching patients about their disease and the lifestyle changes they need to make to help prevent cardiovascular events, and providing a continuum of care, Garrett said.

Patient Adherence

Patient adherence to medication regimens and lifestyle recommendations is a major issue in preventive care, said Lara E. Burke, PhD, MPH, RN, from the University of Pittsburgh.

Studies have shown that only from 20 to 40 percent of patients who are prescribed medications for chronic diseases, such as cardiovascular disease, are still taking their medications one year after the drugs were first prescribed, Dr. Burke said. In addition, from 30 to 50 percent of the drugs prescribed fail to have the desired effect due to lack of adherence.

A number of strategies have helped improve patient adherence, she said, including tailoring the drug regimen to the patient's lifestyle, culture, and needs; asking about adherence at every visit; following up on missed appointments; involving the patient as a member of the cardioteam; simplifying the regimen as much as possible; and counseling the patient about the value of the regimen.

ACC Chapter Receptions

ACC chapters provide a vital link to cardiology at the local level, and Chapter Night is a great way to learn about opportunities to get involved at the local level. The following receptions will be held Monday at the Hyatt Regency McCormick Place:

Alabama	5:30pm - 7:30pm	CC23C
California	5:30pm - 7:30pm	CC12C
Connecticut	5:30pm - 7:30pm	CC20A
Florida	5:30pm - 7:30pm	CC12A
Illinois	5:30pm - 7:30pm	CC11
Indiana	5:30pm - 7:30pm	CC24
Kansas	5:30pm - 7:30pm	CC23A
Kentucky	5:30pm - 7:30pm	CC23C
Louisiana	5:30pm - 7:30pm	CC23C
Maine	5:30pm - 7:30pm	CC21A
Massachusetts	5:30pm - 7:30pm	CC20B
Michigan	5:30pm - 7:30pm	CC10BC
Minnesota	5:30pm - 7:30pm	CC23B
Missouri	5:30pm - 7:30pm	CC23A
Misssissippi	5:30pm - 7:30pm	CC23C
New Hampshire	5:30pm - 7:30pm	CC21A
New Jersey	5:30pm - 7:30pm	CC20C
New York	5:30pm - 7:30pm	CC12B
Ohio	5:30pm - 7:30pm	CC24
Oklahoma	5:30pm - 7:30pm	CC23A
Pennsylvania	5:30pm - 7:30pm	CC24
Rhode Island	5:30pm - 7:30pm	CC21C
Tennessee	5:30pm - 7:30pm	CC23C
Texas	5:30pm - 7:30pm	CC21B
Vermont	5:30pm - 7:30pm	CC21A
Virginia	5:30pm - 7:30pm	CC22B
Washington	5:30pm - 7:30pm	CC22A
West Virginia	5:30pm - 7:30pm	CC24
Wisconsin	5:30pm - 7:30pm	CC22C

ACC BOT Approves Membership Category for Nonphysician Health Care Professionals

The American College of Cardiology (ACC) Board of Trustees (BOT) has approved a plan for the College to create a new membership category for nonphysician health care professionals. The new category is a nonvoting, affiliate membership and is geared toward nonphysician members of the cardiac care team, specifically physician assistants (PAs), nurse practitioners (NPs), and registered nurses (RNs).

The creation of an affiliate membership category in the ACC will be an excellent opportunity for nonphysician health care professionals to formalize their relationship with physicians and promote communication and collaboration with physicians and other members of the cardiac care team, explained ACC President W. Bruce Fye, MD.

"This is an extremely exciting moment fin the College's history," Dr. Fye said. "This initiative has the potential to significantly improve patient care by creating new educational opportunities for and communication among all members of the cardiac care team."

A task force to investigate the issue of expanding membership opportunities in the College was formed in June of last year under the leadership of BOT member Costas Lambrew, MD, director emeritus of the Cardiology Division at the Maine Medical Center in Portland, Maine, and chair of the ACC Allied Health Professionals Committee. The task force coordinated a series of six one-hour telephone "focus group" conference calls with PAs, NPs, and RNs involved in cardiac care to explore their educational needs, professional priorities, and interest in the ACC.

Participants in the conference calls came from a variety of different work environments. Some of them were already part of a well-functioning cardiac care team, while others worked exclusively with one or two cardiologists.

"Overall, the focus group participants were familiar with the ACC and hold the College in high esteem," said Dr. Lambrew. "The majority agreed that the primary need that the College can fill for them is to provide quality, high-level, continuing education for nonphysician health care professionals who specialize in cardiovascular care.

"It is becoming more and more apparent every day that improving patient care means ensuring that the whole cardiac care team is functioning as a cohesive unit," added Dr. Lambrew. "Cardiac care nurses, NPs, and PAs want the same high-level, quality educational content that cardiologists receive from the ACC, and they want to provide quality care to their patients. Expanding membership in the College is an excellent opportunity to achieve both goals."

The potential marketplace of this new

See BOT, page 7

Presidential Plenary Session

Dr. Fye to Address Clinical Trials, Guidelines, and Conflicts of Interest

ACC President W. Bruce Fye, MD, will deliver the annual Presidential Plenary Address this morning at 8 a.m. in Hall D of McCormick Place. Dr. Fye, who at ACC '03 is completing a successful and productive year as the College's president, will call on ACC members to maintain the integrity of the relationship between clinical trials, practice guidelines, and continuing education.

"Powerful scientific and socioeconomic forces continue to transform medical practice and research, especially in this country," Dr. Fye said. "What I call the 'trial-guideline-education process' is having profound effects on cardiology research and practice."

Dr. Fye said that the practice of medicine is undergoing a paradigm shift of unprecedented proportions due to the combined effects of the parallel clinical trial, practice guideline, and continuing education movements.

"Although the trial-guideline-education process has helped to inform decisions and enhance care, it presents some challenges," Dr. Fye said. "I will focus on one: financial conflicts of interest that pose a threat to the vital but vulnerable interface between academic medicine and industry."

Dr. Fye will also touch on the importance of disclosure statements, which he says should be required for activities such as publications and presentations, as well as for other functions like committee and editorial work, "where conflicts might influence outcomes."

Dr. Fye called for common standards to be developed to ensure the integrity of the trial-guideline-education process.

"We can't allow publicity or profit potential to blur our focus on patients or compromise the credibility of the trial-guideline-education process," he said.

"The ACC prides itself on being the premier source of continuing medical education for cardiovascular specialists. This means the College has a special obligation to ensure the integrity of the trial-guideline-education process," Dr. Fye said. "Because the ACC, like other professional societies, depends on industry to help support our mission, we must be alert to the potential for bias."

ACCEL Special Issue on Peripheral Interventions Available

Scientific Session attendees are encouraged to stop by the Medical Simulation Corporation booth (#3242) to receive a complimentary special edition of the College's audiojournal ACCEL. This special edition CD focuses on peripheral interventions and features five interviews with leading cardiovascular specialists. The ACCEL Special Peripheral Interventions CD is provided through a grant from Medical Simulation Corporation.

ACCEL

New Drugs Coating Drug-Eluting Stents

Two new agents being tested in drug-eluting stents, angiopeptin and everolimus, are showing encouraging preliminary results in recent small studies, researchers report.

On Sunday, Vincent On-Hing Kwok, MD, described a study in China of angiopeptin, a synthetic cyclic octa-peptide analogue of somatostatin. Angiopeptin inhibits production of growth hormones including platelet-derived growth factor and epithelial growth factor. A phosphorylcholine "sponge" coating loads the drug onto the stent.

"Angiopeptin inhibits smooth muscle cell proliferation," Dr. Kwok said, "but because it is cytostatic, it does not cause local toxicity."

This first angiopeptin study in humans was conducted at Grantham Hospital, Hong Kong, in collaboration with the Brigham and Women's Hospital, Boston.

In the first 13 patients, minimal lumen diameter improved from 0.69 mm to 3.19 mm, Dr. Kwok said, compared with a pre-procedural reference diameter of 3.23 mm. And six-month studies in the first eight patients showed a late loss of 0.55 mm and late loss index of 0.23 mm.

Quantitative coronary angiography and volumetric intravascular-ultrasound studies in 14 patients with 16 lesions treated with angiopeptin showed the 126 microgram dose as the most promising, compared with the 22 microgram dose used earlier.

Tests are now being planned for stents coated with SSTR-1, a somatostatin analogue that is more human-vascular specific. Dr. Kwok said.

Everolimus in Randomized Study

Animal studies show that the new anti-proliferative agent everolimus binds to cytosolic immunophyllin and inhibits growth-factor driven cell proliferation, said Eberhard Grube, MD, Heart Center, Sieberg, Germany.

In his presentation here Sunday, Dr. Grube described six-month follow-up results of the FUTURE Trial, the first human trial with everolimus. He said 27 patients with severe single-vessel disease were randomized to the everolimus-coated stent, and 15 to the uncoated stents.

"A bioabsorbable polymer matrix is the vehicle in this stent, versus materials in other stents which stay on the stent after the drug is gone," Dr. Grube said. "This minimizes the inflammatory response."

Patients entering the FUTURE trial had lesions between 2.75 and 4.0 mm in diameter, and 18 mm or less in length.

Dr. Grube said six-month angiographic studies showed an 88 percent reduction of in-stent late loss in 26 patients in the treatment group, compared with 12 controls, and an 87 percent reduction in neo-intimal volume.

"These results almost mirror the results with the sirolimus stent," Dr. Grube noted.

Official Notice

ACC Annual Business Meeting Is Today

The annual business meeting of the College will be held today at 9:30 a.m. in Room S101 of McCormick Place.

All Fellows of the College are encouraged to attend this meeting, where the College's president, W. Bruce Fye, MD, will give a report on the state of the College. Elections will also be held for new officers and trustees.

The agenda for the meeting is as follows:

- Introductory remarks by Dr. Fye;
- Reports of the College's secretary, treasurer, and Nominating Committee; and
- New business.

DRUG-ELUTING STENTS

continued from page 1

In the press conference, Dr. Cohen said the use of sirolimus-eluting stents did increase the cost of the initial procedure and hospital cost considerably. The median cost of the procedure for 533 patients randomized to sirolimus-eluting stents was $7,252, compared with $4,395 for the 525 patients in the "placebo" arm who received standard metal stents, a difference of $2,856. When all initial hospital costs were totaled, at $11,345 and $8,464 respectively, the difference of $2,880 was still in favor of standard therapy.

But when the costs incurred from hospital discharge to 12-month followup were calculated—$5,468 for the sirolimus stent and $8,040 for standard care—the total costs for the sirolimus stent added up to $16,813, versus an almost identical $16,504 for the standard stent.

"That difference of only $309, while not statistically significant, is important if applied to the million patients per year who undergo stenting," Dr. Cohen warned.

However, using longer sirolimus-eluting stents than were used in the SIRIUS trial, Dr. Cohen noted, would likely further reduce the need for repeat revascularization when compared to bare metal stents. The combination of a longer stent and the discontinuation of clopidogrel, the SIRIUS researchers analysis found, would actually result in the drug-eluting stent outperforming the bare stent in terms of cost-effectiveness at one year by $96.

Dr. Cohen concluded that the availability of longer stents and improved implantation techniques should further enhance the cost-effectiveness of this technology in the immediate future.

Long-term results favorable

In other trial data presented during Sunday's Late-Breaking Clinical Trials session, Italian researchers said a 12-month followup of the TAXUS-II paclitaxel stent study showed it to be highly effective at one year after implant.

The TAXUS-II trial randomly assigned 536 patients to receive slow-release or moderate-release paclitaxel-eluting coronary stents.

Antonio Colombo, MD, EMO Centro Cuore, Milan, said the beneficial clinical effects reported at six months are sustained at one year.

At 12 months, there was a 21.5 percent rate of major adverse coronary events among the 270 control patients who received bare metal stents, compared with 10.9 percent for the 131 patients receiving a slow-release paclitaxel stent and 9.9 percent for the 130 patients randomized to moderate-release paclitaxel stent.

"Both the slow release and moderate release paclitaxel stents have superior long-term efficacy," Dr. Colombo said. "And an increase of the adverse event-free survival, from six to 12 months, suggests that the paclitaxel stent prevents rather than delays restenosis."

TAXUS-II also studied the effects of discontinuing clopidrogel after six months, and Dr. Colombo said that data support the safety of discontinuing the anticoagulant.

BOT

continued from page 4

membership category is more than 490,000 health professionals.

At its meeting on Saturday, the BOT also voted to:

- Establish a Cardiac Care Team Committee. A physician and nonphysician member would be assigned as committee co-chairs.
- Create educational models that demonstrate the best practices for cardiac care team function and develop vehicles for teaching others how to implement these models in their own institutions.
- Offer educational programs, including Web-based offerings, for nonphysician members of the cardiac care team at the institution/practice, regional, and national levels.
- Develop competency and training statements with members of the cardiac care team.
- Add appropriate members of cardiac care teams to committees/task forces/working groups that are developing materials/tools and systems to bring about compliance with guidelines in their institutions and practices.

Disease Management Programs Focus of Health Policy Symposium

Most experts agree that the collaboration of physicians and industry in evolving the management of chronic disease holds great potential, especially in the area of cardiovascular disease. Many physicians, however, are still skeptical about the use of disease management programs. During this year's Health Policy Symposium, several noted experts will delve into some of the issues surrounding disease management programs.

"Each day physicians face the daunting challenge of managing large numbers of chronically ill patients using increasingly limited resources, while being required to document performance," said Janet Wright, MD, chair of the ACC Disease Management Workgroup, who will moderate the session. "We think the tools available through disease management programs have the potential to help cardiovascular specialists deliver better care to more patients."

During the session, a panel of experts will discuss several key areas of disease management, including an overview of how disease management programs work, a review of the data on DM programs, and a discussion of the major barriers to adoption of DM by the physician community. Presentations will also include highlights on physician and patient views on chronic disease management, provider-based DM success stories, and establishing a frame work for the future of disease management.

"Treatment of Chronic Cardiovascular Disease Management: Is It a Threat or a Solution?" will be held on Tuesday, April 1, from 2 to 3:30 p.m., in room S101 of McCormick Place.

The Health Policy Symposium is supported by unrestricted educational grants from American Healthways, Inc. and Sanofi-Synthelabo, and has been developed in collaboration with the Disease Management Association of America.

Fellowship Candidates

Get Ready for Convocation

The College's Annual Convocation will be held on Tuesday evening, beginning at 6 p.m., in the Grand Ballroom of the Chicago Hilton & Towers. In preparation for the Convocation Ceremony, all Fellowship candidates must sign the Convocation Register, located in the Convocation Office in McCormick Place South, Hall A (next to Registration). The register must be signed by 5 p.m. on Monday. Certificates will be available immediately following the Convocation only for those who sign the register in advance. The Convocation office is open Sunday and Monday from 8 a.m. to 5 p.m. and Tuesday from 8 a.m. to noon.

Child Care During Convocation

During Convocation on Tuesday, the College will provide a complimentary children's activity room from 5:30 to 8 p.m. in the Marquette Room of the Chicago Hilton & Towers. The activity room will be operated on a walk-in basis and will feature children's videos, books, coloring supplies, and games. Children must be accompanied and supervised by a parent or other responsible adult.

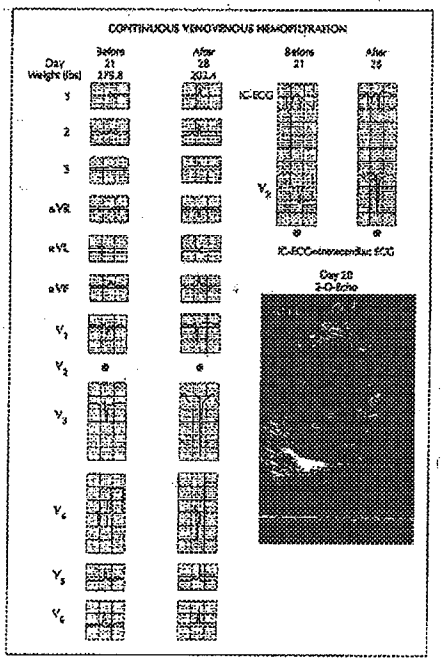
Arrangements for child care can also be made through the front desk or the concierge of most hotels.

Scientific Session News

Registration Issue
Vol. 21, No. 6
March 31, 2003

Scientific Session News is published by the American College of Cardiology Foundation, Department of Communications, 9111 Old Georgetown Road, Bethesda, MD 20814-1699

Journal of the
American College
of Cardiology



Increased QRS voltage with relief of Anasarca

- Presidential Address: Quality of Cardiovascular Care
- Late-Breaking Clinical Trials From ACC 2001
- Vascular Complications With Arteriotomy Closure Devices
- Coronary Artery Disease in South Indians
- Race and Coronary Revascularization Procedure Use
- Obesity and Heart Failure Mortality
- Gender, Myocardial Infarction and Survival

Elsevier
ISSN 0735-1097

Journal of the American College of Cardiology

September 2001

Volume 38

Number 3

CONTENTS IN BRIEF

Journal of the American College of Cardiology (ISSN 0735-1097) is issued monthly, except semimonthly in March, June and November, in two indexed volumes per year by Elsevier Science Inc., 655 Avenue of the Americas, New York, NY 10010. Printed in USA at 500 Cadmus Lane, Easton, MD 21601-0969. Subscription prices per year: For customers in the USA only: institutional rate: US$ 515.00, personal rate: US$ 185.00, student/resident rate: US$ 115.00. For surface mail delivery to customers in Europe, The CIS, and Japan: institutional rate: NLG 868.00 (euro 393.25) for European countries, JPY 54,000; personal rate: NLG 387.00 (euro 266.37) for European countries, JPY 36,900. For surface mail delivery to customers in all other countries: Personal rate: US $ 398.00; institutional rate: US $437.00. For surface airlift delivery to customers in Europe: institutional rate: NLG 1,153.00. For surface airlift to customers in Japan: institutional rate: JPY 72,400. Prices include postage and are subject to change without notice. Periodicals postage paid at New York, NY and at additional mailing offices. Postmaster: Send address changes to *Journal of the American College of Cardiology*, Elsevier Science Inc., 655 Avenue of the Americas, New York, NY 10010.

0735-1097(200109)38:3;1-X

Journal of the American College of Cardiology
© 2001 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 38, No. 3, 2001
ISSN 0735-1097/01/$20.00
PII S0735-1097(01)01458-9

Cutting Balloon Angioplasty for the Treatment of In-Stent Restenosis: A Matched Comparison With Rotational Atherectomy, Additional Stent Implantation and Balloon Angioplasty

Milena Adamian, MD, PHD,† Antonio Colombo, MD, FACC,* Carlo Briguori, MD, PHD,* Takahiro Nishida, MD,* Federica Marsico, MD,* Carlo Di Mario, MD, PHD, FACC,* Remo Albiero, MD,* Issam Moussa, MD,† Jeffrey W. Moses, MD, FACC†

Milan, Italy, and New York, New York

OBJECTIVES The purpose of the study was to determine whether cutting balloon angioplasty (CBA) has advantages over other modalities in treatment of in-stent restenosis (ISR).

BACKGROUND Controversies exist regarding optimal treatment for ISR. Recently, CBA emerged as a tool in management of ISR.

METHODS A total of 648 lesions treated for ISR were divided into four groups according to the treatment strategy: CBA, rotational atherectomy (ROTA), additional stenting (STENT), and percutaneous transluminal coronary angioplasty (PTCA). Following the matching process, 258 lesions were entered into the analysis.

RESULTS Baseline clinical and angiographic characteristics were similar among the groups (p = NS). Acute lumen gain was significantly higher in the STENT group (2.12 ± 0.7 mm), whereas in the CBA group the gain was similar to one achieved following ROTA and following PTCA (1.70 ± 0.6 vs. 1.79 ± 0.5 mm and 1.56 ± 0.7 mm, respectively; p = NS). The lumen loss at follow-up was lower for the CBA versus ROTA and versus STENT (0.63 ± 0.6 vs. 1.30 ± 0.8 mm and 1.36 ± 0.8 mm, respectively; $p < 0.0001$), yielding a lower recurrent restenosis rate (20% vs. 35.9% and 41.4%, respectively; $p < 0.05$). By multivariate analysis, CBA (odds ratio [OR] = 0.17; confidence interval [CI], 0.06 to 0.51; $p = 0.001$) and diffuse restenosis type at baseline (OR = 2.07; CI, 1.15 to 3.71; $p = 0.02$) were identified as predictors of target lesion revascularization.

CONCLUSIONS We conclude that CBA is a safe and efficient technique for treatment of ISR, with immediate results similar to atheroablation and better clinical and angiographic outcomes at follow-up. This approach might be implemented as a viable option in management of focal ISR and to prepare diffuse ISR for brachytherapy treatment. (J Am Coll Cardiol 2001;38:672–9) © 2001 by the American College of Cardiology

With the expanded application of coronary stenting beyond the criteria for inclusion in the randomized trials, stent restenosis emerged as a new "disease entity." With over 800,000 stents a year in the U.S., and a stent restenosis incidence of 20% to 50% of lesions, it becomes clear that in-stent restenosis (ISR) is a significant problem (1). The most common modality to treat ISR is percutaneous transluminal coronary angioplasty (PTCA), but long-term results are unsatisfactory, with a high recurrence rate, particularly after treatment of diffuse (lesion length >10 mm) ISR (2). Additional stent implantation (STENT) may have

See page 680

merit because it reduces acute recoil and helps tissue extrusion; however, this acute benefit did not translate into improved long-term outcome (3–5). Atheroablative therapies (i.e., rotational atherectomy [ROTA] and excimer laser angioplasty) have been used in an attempt to decrease the rate of recurrence. However, the beneficial effect of these devices was not proven (6). Recent reports suggested that cutting balloon angioplasty (CBA) might be of benefit in the treatment of ISR, decreasing the need for repeat revascularization procedures (7,8).

The aim of our study was to compare acute and long-term angiographic and clinical outcomes between the various techniques that have been used to treat ISR in matched lesion subsets.

METHODS

Patient and lesion characteristics. Between January 1997 and February 1999, a total of 1,410 patients (1,980 lesions) underwent successful coronary stent implantation at Centro Cuore Columbus, Milan, Italy. Out of this population, 684 lesions (38%) had ISR. These lesions were divided into four groups based on the ISR treatment modality: PTCA, STENT, ROTA and CBA. The groups were matched according to clinical and angiographic characteristics: presence of diabetes mellitus, reference vessel size, minimal lumen diameter (MLD), lesion length and type of ISR.

From the *EMO Centro Cuore Columbus, Milan, Italy, and the †Lenox Hill Heart and Vascular Institute, New York, New York. No financial support was received for this study.

Manuscript received January 23, 2001; revised manuscript received April 27, 2001, accepted June 8, 2001.

JACC Vol. 38, No. 3, 2001
September 2001:672–9

Abbreviations and Acronyms

CABG	= coronary artery bypass graft surgery
CBA	= cutting balloon angioplasty
CI	= confidence interval
CK	= creatine kinase
CK-MB	= creatine kinase-myocardial band
ISR	= in-stent restenosis
IVUS	= intravascular ultrasound
MACE	= major adverse cardiac events
MI	= myocardial infarction
MLD	= minimal lumen diameter
NQMI	= non–Q-wave myocardial infarction
OR	= odds ratio
PTCA	= percutaneous transluminal coronary angioplasty
QCA	= quantitative coronary angiography
QMI	= Q-wave myocardial infarction
ROTA	= rotational atherectomy
STENT	= additional stenting
TLR	= target lesion revascularization

Following the matching process and the random selection of only one lesion per patient, the final patient population totaled 258 (258 lesions). The numbers of patients/lesions in each group were: CBA, 57; ROTA, 48; STENT, 79; and PTCA, 74.

Angiographic follow-up was obtained in 85% of the eligible patients at an average duration of 6.2 ± 3.2 months. Clinical follow-up was obtained through outpatient clinic visits, by direct telephone interview and with the referring physician when additional information was necessary. Clinical follow-up was obtained in 100% of patients at an average of 11 ± 8 months.

PROCEDURE

Before angioplasty, 70 U/kg of intravenous heparin and 0.2 mg nitroglycerin intracoronary were administered. All patients received aspirin 300 mg q.d. and ticlopidine 250 mg b.i.d. starting three days before the procedure when feasible. Each operator selected a particular procedure according to his judgment. In general, we can state that ROTA, PTCA and stenting were used more frequently in the early period while CBA was used more recently. Each patient was encouraged to return for angiographic follow-up between the fifth and sixth month following the procedure.

Cutting balloon angioplasty. Cutting balloon (InterVentional Technologies, San Diego, California) is a conventional balloon catheter 10 or 15 mm in length with three (on smaller balloon sizes) or four microblades (on balloon sizes >3.5 mm in diameter). These blades, mounted longitudinally on the surface of balloon, are ~0.25 mm in height and three to five times sharper than conventional surgical blades (9). During dilation, the device produces three or four endovascular surgical incisions. The CBA was performed with multiple inflations, increasing the balloon pressure, usually up to 12 atm.

ROTA with adjunct balloon angioplasty. The techniques used for ROTA have been described elsewhere (6,10). Rotablator or Rotalink devices (Boston Scientific, Scimed, Maple Grove, Minnesota) were used with an incremental burr size approach to achieve a burr/artery ratio ≥0.7. After ROTA, adjunct PTCA was routinely performed with balloon-to-artery ratio of 1:1 utilizing medium to high pressure (12 to 16 atm).

Additional stent implantation. Restenotic lesions treated by additional stent implantation were predilated using a traditional balloon angioplasty. If necessary, multiple stents were used to cover the entire lesion. Postdilation was performed with an appropriately sized balloon at high pressure (≥14 atm).

PTCA. The PTCA procedure was done using noncompliant or semicompliant balloons that matched the size of the final balloon used at the time of stent implantation. Single or multiple high-pressure balloon inflations (≥12 atm) were generally performed with the goal of achieving a near 0% residual stenosis. A larger balloon (0.5 mm) than the original postdilation balloon was used at the operator's discretion if the stent was considered undersized compared to the reference vessel size.

Intravascular ultrasound evaluation. Intravascular ultrasound (IVUS) was performed only in situations where a possible stent underexpansion was thought to be present. On average, IVUS was used in 21%, 22%, 24%, and 34% in CBA, ROTA, STENT and PTCA groups, respectively (p = NS).

Definitions. *In-stent restenosis* was defined as >50% diameter stenosis by quantitative coronary angiography (QCA) inside the stent or within 5 mm from the edges of a stented lesion presenting at least eight weeks after the stent implantation. In addition, ISR was defined as focal (<10 mm in length) or diffuse (>10 mm in length).

Major adverse cardiac events (MACE) were defined as death, any myocardial infarction (MI) and/or repeat revascularization (coronary artery bypass graft surgery [CABG]/repeat PTCA). A diagnosis of *Q-wave myocardial infarction* (QMI) was made when there was documentation of new pathologic Q-waves (>0.04 s) on an electrocardiogram in conjunction with an elevation of total creatine kinase (CK) more than twice the normal value, with a concomitant elevation of creatine kinase-myocardial band. A diagnosis of *non–Q-wave myocardial infarction* (NQMI) was made when an elevation of total CK to greater than twice the upper limit of normal value, with a concomitant elevation of CK-MB, was documented without development of new pathologic Q-waves. *Procedural success* was defined as achievement of a residual diameter stenosis <30% at the lesion site without the occurrence of death, bypass surgery, or QMI. Recurrent restenosis at follow-up angiography was defined as ≥50% diameter stenosis by quantitative coronary angiography (QCA) occurring not earlier than eight weeks after successful treatment of ISR.

Table 1. Baseline Demographic Characteristics

	CBA (n = 57)	ROTA (n = 48)	STENT (n = 79)	PTCA (n = 74)	p Value
Age, (yrs)	59.9 ± 9.0	59.3 ± 10.1	59.6 ± 9.2	61.3 ± 10.8	0.87
Male gender, n (%)	48 (84)	42 (88)	71 (90)	66 (89)	0.84
Unstable angina, n (%)	9 (16.4)	10 (20.8)	14 (17.7)	12 (16.2)	0.56
Elevated cholesterol, n (%)	40 (70.2)	30 (63)	42 (53.8)	40 (54.1)	0.05
Hypertension, n (%)	27 (47)	23 (48)	41 (52)	39 (53)	0.98
Diabetes, n (%)	8 (14)	4 (8.3)	9 (11.3)	7 (9.5)	0.73
Multivessel CAD, n (%)	32 (56.1)	33 (70.2)	41 (52.6)	51 (68.9)	0.07
LV ejection fraction (%)	60.7 ± 12.9	63.3 ± 9.6	60.3 ± 13.7	62.2 ± 11.9	0.17

CAD = coronary artery disease; CBA = cutting balloon angioplasty; LV = left ventricular; PTCA = percutaneous transluminal coronary angioplasty; ROTA = rotational atherectomy; STENT = additional stenting.

QCA. For each lesion, the single view showing the most severe degree of stenosis was used for QCA with a computer-assisted automated edge detection algorithm (QCA-CMS version 4.0, MEDIS, Leiden, the Netherlands). Both absolute reference and MLD in millimeters were determined using the guiding catheter filled with contrast for calibration. The lesion length was measured as the distance from shoulder to shoulder. In complex lesions with the involvement of adjacent segments proximal and distal, a user-defined reference lumen diameter of a proximal and distal angiographically normal-appearing segment was chosen.

Acute lumen gain was defined as the MLD immediately after the procedure minus the MLD before the procedure. *Late lumen loss* was defined as the MLD after the procedure minus the MLD at follow-up. The *late-loss index* was defined as the late lumen loss divided by the acute lumen gain.

Matching process. Matching was performed by a computerized program and was based on principles of the matching process derived from Umans et al. (11). The database was reviewed sequentially; for each restenotic lesion treated with the cutting balloon, the first lesion encountered in each of the three different treatment groups (ROTA, STENT, CBA) that satisfied the matching parameters was chosen. The matching parameters in order of sequential selection were: 1) diabetes; 2) reference diameter ± 0.3 mm; 3) baseline MLD ± 0.1 mm; 4) lesion length ± 1 mm; and 5) type of restenosis. The order we selected to perform the lesion selection for the matching process influenced the parameter, which could not always find a corresponding lesion with the same parameter.

Statistical analysis. Statistical analysis was performed using the StatView statistical package (StatView 5, SAS Institute, Cary, North Carolina). To remove any confounding factor due to the behavior of different lesions in the same patient, we used the patients as the unit of the analysis. For patients with multiple lesions, only one randomly selected lesion was included in the analysis according to the following randomization scheme; each lesion was assigned a random number between 0 and 1. The lesion corresponding to the smallest number was included in the analysis.

Comparison among the groups was performed by the χ^2 test (or the Fisher exact test) for categorical data. A value of $p < 0.05$ was considered statistically significant. The analysis of variance test was performed for continuous data. Multiple comparisons were accounted for by using the Bonferroni-Dunn method to preserve the overall significance level. Results were expressed as mean value ± SD. Independent risk factors were determined using a multivariate logistic regression model. Results were presented as the odds ratio (OR) and 95% confidence interval (CI) for each variable. Values with a significance level of $p < 0.05$ were accepted as significant.

RESULTS

Patient characteristics and procedural outcome. There was no difference in the baseline clinical and lesion characteristics among the four groups (Tables 1 and 2). Procedural success was achieved in all patients in the CBA group, whereas there were one NQMI in the ROTA group, two QMIs in the STENT group, and three events in the PTCA group (1 death; 1 emergency CABG; and 1 QMI). However, the difference in incidence of in-hospital MACE among the four groups did not reach statistical significance.

Angiographic analysis. Quantitative angiographic measurements, both pre- and postintervention and at follow-up, are summarized in Table 2. No significant differences were seen in baseline angiographic measurements among the four groups. After intervention, the greatest MLD was achieved in the STENT group, without statistical significance, compared to the ROTA and CBA groups. Lesions treated with PTCA alone had the smallest final MLD. In the STENT group, the balloon was inflated at a higher pressure (15.7 ± 3.9 atm) than in the CBA group (10.7 ± 2.8 atm, $p < 0.0001$). A significantly higher late loss at follow-up was observed in the ROTA, STENT, and PTCA groups (1.30 ± 0.8 mm vs. 1.36 ± 0.8 mm vs. 1.07 ± 0.8, respectively) compared to the CBA group (0.63 ± 0.7 mm; $p < 0.0001$). In addition, the loss index was significantly lower in the group of lesions treated with CBA (0.38 ± 0.3 mm) than in the other groups.

Long-term clinical outcome. The mean duration of clinical follow-up was 11 ± 8 months. Death, CABG and MI occurred with equal proportions in all groups (Table 3).

JACC Vol. 38, No. 3, 2001
September 2001:672-9

Table 2. Lesion and Angiographic Characteristics

	CBA (n = 57)	ROTA (n = 48)	STENT (n = 79)	PTCA (n = 74)	p Value
Vessel treated, n (%)					
LAD	21 (36.8)	24 (50)	28 (35.4)	28 (37.8)	0.8
LCX	8 (14)	10 (20.8)	11 (13.9)	10 (13.5)	
RCA	18 (31.6)	9 (18.8)	25 (31.6)	24 (32.4)	
LMCA	2 (3.5)	1 (2.1)	1 (1.3)	2 (2.7)	
	7 (12.3)	4 (8.3)	10 (12.7)	8 (10.8)	
Restenosis type, n (%)					
Diffuse	20 (35.1)	21 (43.8)	23 (29.1)	26 (35.1)	0.2
Focal	36 (63.2)	25 (52.1)	49 (62)	40 (54.1)	
Occluded	1 (1.8)	2 (4.2)	7 (8.9)	8 (10.8)	
Reference vessel diameter (mm)	2.89 ± 0.5	2.95 ± 0.4	2.91 ± 0.5	2.90 ± 0.5	0.9
Pre-MLD (mm)	0.8 ± 0.4	0.78 ± 0.4	0.78 ± 0.5	0.84 ± 0.5	0.8
% Diameter stenosis	72.4 ± 12.9	73.5 ± 13.9	73.6 ± 16.3	70.9 ± 15.1	0.7
Lesion length (mm)	13.4 ± 6.5	16.3 ± 10.3	14.3 ± 8.9	14.9 ± 9.5	0.4
Final MLD (mm)	2.5 ± 0.5	2.57 ± 0.6	2.90 ± 0.6	2.40 ± 0.6	<0.001‡¶#
Final % stenosis	18.1 ± 11.2	17.8 ± 12.2	6.2 ± 3.3	20.2 ± 3.9	<0.0001‡¶#
MLD at follow-up (mm)	1.87 ± 0.7	1.27 ± 0.9	1.54 ± 0.9	1.33 ± 0.8	0.01*†‡#
Acute gain (mm)	1.7 ± 0.6	1.79 ± 0.5	2.12 ± 0.7	1.56 ± 0.7	<0.0001‡§¶#
Late loss (mm)	0.63 ± 0.6	1.30 ± 0.8	1.36 ± 0.8	1.07 ± 0.8	<0.0001*†‡§¶
Loss index	0.38 ± 0.3	0.73 ± 0.6	0.64 ± 0.4	0.89 ± 0.6	<0.0003*†‡
Procedural success (%)	100	98.7	98.8	97.5	NS
Balloon/vessel ratio	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	NS
MIP, atm	10.7 ± 2.8	12.9 ± 4.2	15.7 ± 3.9	13.1 ± 4	<0.0001*†‡¶#

*p < 0.05 for CBA vs. PTCA; †p < 0.05 for CBA vs. ROTA; ‡p < 0.05 for CBA vs. STENT; §p < 0.05 for PTCA vs. ROTA; ¶p < 0.05 for PTCA vs. STENT; #p < 0.05 for ROTA vs. STENT.

LAD = left anterior descending artery; LCX = left circumflex artery; LMCA = left main coronary artery; MIP = maximum inflation pressure; MLD = minimal lumen diameter; RCA = right coronary artery. Other abbreviations as in Table 1.

Recurrent ISR rate was significantly lower in the CBA group compared to other groups (CBA, 20%; ROTA, 35.9%; STENT, 41.4%; and PTCA, 45.2%; p = 0.04) with a significantly lower target lesion revascularization (TLR) rate (CBA, 15.8%; ROTA, 31.9%; STENT, 35.5%; and PTCA, 37.8%; p = 0.03). A diffuse pattern of recurrence was more common in lesions treated with PTCA, whereas focal pattern of recurrence was more common in the CBA group (Table 3).

Predictors of TLR. By univariate analysis, the presence of final MLD, diffuse ISR at baseline, and CBA were all identified as risk factors of TLR. However, in the multivariate model, CBA (OR 0.33; p = 0.003) and diffuse pattern of ISR at baseline (OR 2.07; p = 0.02) were distinguished as predictors of repeat revascularization procedures at follow-up (Table 4).

Using logistic regression analysis we also looked for factors triggering the occurrence of diffuse recurrent restenosis. Using multivariate analysis, the diffuse character of the initial ISR and treatment with PTCA were identified as independent predictors of recurrence of diffuse ISR.

DISCUSSION

The results of our study indicate that CBA can be safely used to treat ISR with acceptable acute angiographic and

Table 3. Clinical and Angiographic Outcomes

	CBA (n = 57)	ROTA (n = 48)	STENT (n = 79)	PTCA (n = 74)	p Value
In-hospital MACE, n (%)	0	1 (2.1)	2 (2.5)	3 (4.1)	NS
Acute closure, n (%)	0	1 (2.1)	0	1 (1.4)	NS
MACE at follow-up, n (%)*	10 (17.5)	17 (35.4)	30 (37.9)	32 (43.2)	0.01
Death (n)	1	1	2	1	NS
MI (n)	0	0	1	2	NS
TLR, n (%)*	9 (15.8)	15 (31.9)	27 (35.5)	28 (37.8)	0.03
Angiographic follow-up, n (%)	45 (79)	39 (81)	69 (87)	63 (85)	NS
Recurrent restenosis, n (%)*	9 (20)	15 (35.9)	29 (41.4)	28 (45.2)	0.04
Re-restenosis type, n (%)					
Diffuse	3 (33.3)	4 (33.3)	10 (34.5)	19 (73.1)	0.002
Focal	6 (66.7)	8 (66.7)	19 (65.5)	7 (26.3)	

*p < 0.05 for CBA vs. ROTA, STENT, PTCA comparisons. p = NS for comparisons among ROTA, STENT, and PTCA.

MACE (major adverse cardiac events) = death, Q-wave myocardial infarction (MI), coronary artery bypass graft/repeat PTCA. TLR = target lesion revascularization. Other abbreviations as in Table 1.

Table 4. Predictors of Long-Term Outcomes

Variable	Univariate OR (95% CI)	p Value	Multivariate OR (95% CI)	p Value
Predictors of target lesion revascularization				
CBA	0.34 (0.16–0.73)	0.006	0.17 (0.06–0.51)	0.001
Diffuse restenosis at baseline	2.34 (1.34–4.09)	0.003	2.07 (1.15–3.71)	0.02
Final MLD	0.59 (0.38–0.93)	0.02		
Predictors of recurrent diffuse restenosis				
PTCA	6.33 (2.20–18.22)	0.0006	7.81 (2.10–29.10)	0.002
Diffuse restenosis at baseline	4.8 (1.72–13.42)	0.003	6.3 (1.77–22.6)	0.005
Final MLD	0.27 (0.13–0.57)	0.0006		

CBA = cutting balloon angioplasty; CI = confidence interval; MLD = minimal lumen diameter; OR = odds ratio; PTCA = percutaneous transluminal coronary angioplasty.

clinical outcome. Moreover, CBA significantly decreases the rate of repeat revascularization procedures at follow-up compared to other commonly used techniques for management of ISR.

Current treatment of ISR. In contrast to angioplasty, where restenosis is predominantly caused by elastic recoil and vascular remodeling, ISR is almost exclusively due to neointimal hyperplasia (12,13). Although the optimal treatment of ISR has not yet been well defined, three treatment approaches are commonly used: 1) PTCA; 2) atheroablation (ROTA, excimer laser angioplasty [ELCA] and directional coronary atherectomy); and 3) STENT. Recently, brachytherapy has been effectively used to prevent angiographic and clinical recurrence following optimal mechanical dilation (14). Most of the studies comparing different treatment strategies for ISR were not randomized or matched comparisons. Of importance is that not all ISR lesions have a similar risk of recurrence (15).

The simplest way to treat ISR is repeat dilation using a conventional PTCA balloon. Mechanism of lumen enlargement after PTCA for ISR is controversial. Although Gordon et al. (16) attributed it to neointimal tissue compression and extrusion of out-of-stent struts, an IVUS study by Mehran et al. (17) showed that tissue extrusion and additional stent expansion contributed equally to lumen improvement. In the Mehran et al. study, there was 32% of residual neointimal tissue of the stent area following PTCA.

In general, recurrence after PTCA treatment of ISR has been reported to range from 37% to 50% (angiographic restenosis) and from 14% to 30% (clinical restenosis) (2,17–19).

In our series, PTCA treatment gave the lowest acute gain (1.56 ± 0.7 mm) with a late loss of 0.89 ± 0.6 mm at follow-up associated with the highest rates of angiographic and clinical recurrence (45.2% and 41.4%, respectively). In the past we reported better long-term results following PTCA for ISR with a target vessel revascularization of 11% (19). The discordance between the results of the current study and our former report can be explained by the larger reference vessel size, the shorter lesion length, and the very low angiographic follow-up rate reported in that study.

Atheroablative techniques have been used in an attempt to improve the acute results of PTCA by increasing lumen dimensions through ablation of neointimal tissue (20,21). Clinical recurrence after ROTA has ranged from 28% to 50%, with an angiographic restenosis rate up to 45% (10,22–24). In one study (25), 28% of TLRs occurred after ROTA with adjunctive PTCA versus 46% with PTCA alone.

In another study, vom Dahl et al. (6) recently reported that the occurrence of re-restenosis correlated with length of the primarily stented lesion and was as high as 49% (TLR, 35%) for long diffuse lesions treated with ROTA and adjunctive balloon angioplasty. A subsequent randomized study confirmed the lack of additional benefit of ROTA and adjunctive PTCA versus simple angioplasty (26).

Preliminary observations indicate that additional stent implantation achieves the best acute results (QCA diameter stenosis of 10%) by recovering all the lumen area of the original stenting procedure, primarily via neointimal tissue extrusion out of the stent, with some additional stent expansion (5,18). However, angiographic recurrence after additional stent implantation has ranged from 30% to 35%, with clinical recurrence from 17% to 40% (3,4). The highest acute gain and the largest acute MLD were obtained after STENT. However, these acute results were offset by a high late lumen loss (about 47%) at follow-up. Different amounts of net gain obtained with PTCA, STENT and ROTA may explain the different angiographic and clinical restenosis rates. A comparison of PTCA, ELCA, ROTA and STENT in a large series of 821 restenotic lesions was concluded with the statement that "all interventional strategies are disappointing," demonstrating similar late clinical outcome independent of device choice (27).

CBA. The cutting balloon catheter is a relatively novel device. The concept of CBA rests on the presence of microblades intended to incise the atherosclerotic plaque or neointimal tissue at the beginning of balloon inflation and to develop a controlled fault line along which dilation will occur (9). The main application of CBA was in noncalcified lesions with concentric plaque; however, this technique was subsequently applied effectively to treat several types of lesions including ISR (8,28). The Japanese Multicenter Registry of CBA for ISR reported data on 194 lesions

JACC Vol. 38, No. 3, 2001
September 2001:672-9

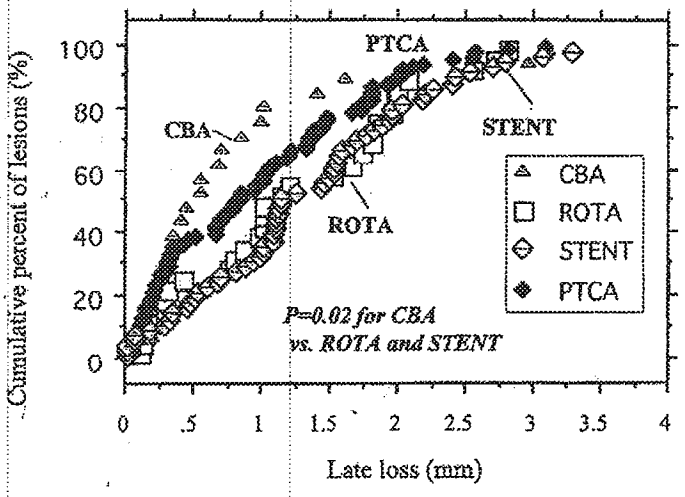


Figure 1. Cumulative frequency distribution of the late lumen loss at follow-up in cutting balloon angioplasty (CBA), percutaneous transluminal coronary angioplasty (PTCA), rotational atherectomy (ROTA), and additional stenting (STENT) groups. Significantly lower lumen loss noticed in CBA group compared to ROTA and STENT groups (0.63 ± 0.6 mm, 1.30 ± 0.8 mm, and 1.36 ± 0.8 mm; $p < 0.0001$).

treated. Angiographic restenosis occurred in 29% and target lesion revascularization in 22% of the lesions (29). These findings are consistent with those reported by Chevalier et al. (7) demonstrating better acute and follow-up angiographic results in treatment of ISR when CBA is compared to PTCA. The acute gain obtained was significantly bigger in the CBA group compared to the PTCA group (2.1 ± 0.47 mm vs. 1.74 ± 0.58 mm; $p < 0.05$). The TLR at nine months was 12% in the CBA group (7). In our series, despite the fact that lumen size immediately after CBA was not as large as after additional stent implantation or ROTA with adjunctive PTCA, follow-up MLD in the CBA group was significantly larger compared to those obtained with other techniques (Fig. 1). Both late lumen loss and loss index were significantly lower in the CBA group compared to the other techniques, resulting in a lower angiographic restenosis rate (20%) and need for TLR (15.7%).

The possible mechanisms for dilation with CBA for ISR are probably related to plaque extrusion through the stent's struts (30,31) compared to other techniques, possibly, with

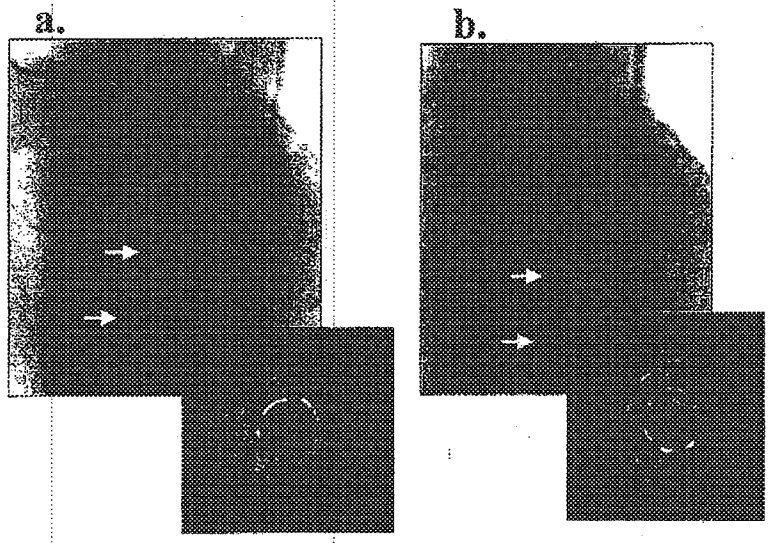


Figure 2. Acute angiographic and intravascular ultrasound (IVUS) results obtained after cutting balloon angioplasty (CBA) for in-stent restenosis (ISR) in left circumflex artery. (a) Preintervention IVUS image shows complete neointimal filling of the lumen in the stent (lumen cross-sectional area 1.3 mm^2). (b) Final result following CBA with 2.5-mm balloon (lumen cross-sectional area 6.0 mm^2).

less tissue injury. Figure 2 demonstrates a typical IVUS finding following CBA for ISR. Another added advantage of the technique of CBA for ISR is the lack of occurrence of the "watermelon seeding effect." This fact could become a problem when contemplating additional brachytherapy, a setting where there is the need to carefully control the boundaries of the injured segment.

Predictors of recurrent ISR. Various investigators reported a recurrence rate following treatment of ISR of between 31% and 85% with relation to the focal or diffuse type of original restenosis (2,6,22).In our study, use of CBA predicted a lower recurrence rate of restenosis but did not predict a lower occurrence of diffuse ISR at the time of the second recurrence. For this reason, and, more importantly, for the high frequency of focal ISR at baseline, we caution to state that CBA could be a viable solution to the problem of diffuse ISR. The important and positive features of the CBA approach for diffuse ISR are to provide a reasonable large final lumen even in large vessels, with no need to use a large guiding catheter, with a lower risk of distal embolization compared to ROTA or directional atherectomy, with the possibility to select carefully the length of the injury segment, and with very limited need for additional stent implantation. When dealing with a diffuse or proliferative ISR, the CBA approach seems the most logical way to prepare the lesion for a more definite therapy such as brachytherapy (32).

Study limitations. There are several limitations to the present study. It is a retrospective study and therefore inherently contains all the disadvantages of such a comparative analysis. The matching process was performed only for a certain set of variables, and this technique may suffer from biases of retrospective evaluations. There were no data regarding IVUS assessment of the treated lesions so as to understand better the mechanism of CBA in ISR.

Conclusions. Finally, CBA seems to be a reasonable approach for patients with ISR. This technique provides immediate results superior to simple angioplasty and quite similar to more complex and expensive atheroablative techniques. Follow-up results do not seem to penalize the CBA approach by a higher late loss compared to other approaches.

We believe that this technique can be considered a reasonable first line and possible definite approach for most focal ISRs and for the preparation of diffuse ISR to other more definite treatment modalities. To evaluate better the definite value of CBA versus PTCA to treat ISR, a randomized study has recently been launched in Europe.

Reprint requests and correspondence: Dr. Antonio Colombo, EMO Centro Cuore Columbus, Via M. Buonarroti 48, 20145 Milan, Italy. E-mail: columbus@micronet.it.

REFERENCES

1. Baim DS, Levine MJ, Leon MB, Levine S, Ellis SG, Schatz RA. Management of restenosis within the Palmaz-Schatz coronary stent (the U.S. multicenter experience). The U.S. Palmaz-Schatz Stent Investigators. Am J Cardiol 1993;71:364–6.
2. Elezi S, Kastrati A, Hadamitzky M, Dirschinger J, Neumann FJ, Schomig A. Clinical and angiographic follow-up after balloon angioplasty with provisional stenting for coronary in-stent restenosis. Cathet Cardiovasc Interv 1999;48:151–6.
3. Elezi S, Kastrati A, Hadamitzky M, Dirschinger J, Neumann FJ, Schomig A. Clinical and angiographic follow-up after balloon angioplasty with provisional stenting for coronary in-stent restenosis. Cathet Cardiovasc Interv 1999;48:151–6.
4. Al-Sergani HS, Ho PC, Nesto RW, et al. Stenting for in-stent restenosis: a long-term clinical follow-up. Cathet Cardiovasc Interv 1999;48:143–8.
5. Antoniucci D, Valenti R, Moschi G, et al. Stenting for in-stent restenosis. Cathet Cardiovasc Interv 2000;49:376–81.
6. vom Dahl J, Radke PW, Haager PK, et al. Clinical and angiographic predictors of recurrent restenosis after percutaneous transluminal rotational atherectomy for treatment of diffuse in-stent restenosis. Am J Cardiol 1999;83:862–7.
7. Chevalier B, Guyon P, Glatt B. Treatment of in-stent restenosis: short- and mid-term results of a pilot study between balloon and cutting balloon (abstr). J Am Coll Cardiol 1999;33:62A.
8. Kurbaan AS, Foale RA, Sigwart U. Cutting balloon angioplasty for in-stent restenosis. Cathet Cardiovasc Interv 2000;50:480–3.
9. Barath P, Fishbein MC, Vari S, Forrester JS. Cutting balloon: a novel approach to percutaneous angioplasty. Am J Cardiol 1991;68:1249–52.
10. Radke PW, Klues HG, Haager PK, et al. Mechanisms of acute lumen gain and recurrent restenosis after rotational atherectomy of diffuse in-stent restenosis: a quantitative angiographic and intravascular ultrasound study. J Am Coll Cardiol 1999;34:33–9.
11. Umans VA, Keane D, Quaedvlieg P, Serruys PW. Matching to guide the design and predict the outcome of randomized atherectomy trials. Am Heart J 1995;130:1135–43.
12. Hoffmann R, Mintz GS, Dussaillant GR, et al. Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study. Circulation 1996;94:1247–54.
13. Kornowski R, Mintz GS, Kent KM, et al. Increased restenosis in diabetes mellitus after coronary interventions is due to exaggerated intimal hyperplasia. A serial intravascular ultrasound study. Circulation 1997;95:1366–9.
14. Kastrati A, Schomig A, Elezi S, et al. Predictive factors of restenosis after coronary stent placement. J Am Coll Cardiol 1997;30:1428–36.
15. Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. Circulation 1999;100:1872–8.
16. Gordon PC, Gibson CM, Cohen DJ, Carrozza JP, Kuntz RE, Baim DS. Mechanisms of restenosis and redilation within coronary stents—quantitative angiographic assessment. J Am Coll Cardiol 1993;21:1166–74.
17. Mehran R, Mintz GS, Popma JJ, et al. Mechanisms and results of balloon angioplasty for the treatment of in-stent restenosis. Am J Cardiol 1996;78:618–22.
18. Baeters C, Banos JL, Van Belle E, McFadden EP, Lablanche JM, Bertrand ME. Six-month angiographic outcome after successful repeat percutaneous intervention for in-stent restenosis. Circulation 1998;97:318–21.
19. Reimers B, Moussa I, Akiyama T, et al. Long-term clinical follow-up after successful repeat percutaneous intervention for stent restenosis. J Am Coll Cardiol 1997;30:186–92.
20. Lee SG, Lee CW, Cheong SS, et al. Immediate and long-term outcomes of rotational atherectomy versus balloon angioplasty alone for treatment of diffuse in-stent restenosis. Am J Cardiol 1998;82:140–3.
21. Mahdi NA, Pathan AZ, Harrell L, et al. Directional coronary atherectomy for the treatment of Palmaz-Schatz in-stent restenosis. Am J Cardiol 1998;82:1345–51.
22. Mehran R, Dangas G, Mintz GS, et al. Treatment of in-stent restenosis with excimer laser coronary angioplasty versus rotational

JACC Vol. 38, No. 3, 2001
September 2001:672–9

atherectomy: comparative mechanisms and results. Circulation 2000; 101:2484–9.
23. Sharma SK, Duvvuri S, Dangas G, et al. Rotational atherectomy for in-stent restenosis: acute and long-term results of the first 100 cases. J Am Coll Cardiol 1998;32:1358–65.
24. Goldberg SL, Berger P, Cohen DJ, et al. Rotational atherectomy or balloon angioplasty in the treatment of intra-stent restenosis: BARASTER multicenter registry. Cathet Cardiovasc Interv 2000;51: 407–13.
25. Dauerman HL, Baim DS, Cutlip DE, et al. Mechanical debulking versus balloon angioplasty for the treatment of diffuse in-stent restenosis. Am J Cardiol 1998;82:277–84.
26. Vom Dahl J, Silber S, Buerttner H, et al. Rotational atherectomy versus balloon angioplasty for diffuse in-stent restenosis: preliminary results of a randomized multicenter trial (ARTIST trial) (abstr). Am J Cardiol 1999;84 Suppl 6A:237.
27. Mehran R. In-stent restenosis: "The great equalizer"—disappointing outcomes with all interventional strategies (abstr). J Am Coll Cardiol 1999;33:63A.
28. Kurbaan AS, Kelly PA, Sigwart U. Cutting balloon angioplasty and stenting for aorto-ostial lesions. Heart 1997;77:350–2.
29. Nakamura M, Matsubara T. Results of cutting balloon angioplasty for stent restenosis. Japanese Multicenter Registry (abstr). J Am Coll Cardiol 1998;31:239A.
30. Albiero R, Nishida T, Karvouni E, et al. Cutting balloon angioplasty for the treatment of in-stent restenosis. Cathet Cardiovasc Interv 2000;50:452–9.
31. Kinoshita Y, Matsuno Y, Ohta T, et al. Dilatation mechanism of cutting balloon angioplasty for in-stent restenosis: comparison with plain old balloon angioplasty using volumetric intravascular ultrasound analysis (abstr). Am J Cardiol 2000;86 Suppl 8A:120i.
32. Teirstein PS, Massullo V, Jani S, et al. Three-year clinical and angiographic follow-up after intracoronary radiation: results of a randomized clinical trial. Circulation 2000;101:360–5.

The New England Journal of Medicine

Established in 1812 as The NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

VOLUME 329 JULY 22, 1993 NUMBER 4

The New England Journal of Medicine (ISSN 0028-4793) is published weekly from editorial offices at 10 Shattuck Street, Boston, MA 02115-6094. Subscription price: $[illegible] per year. Second-class postage paid at Boston and at additional mailing offices. POSTMASTER: Send address changes to P.O. Box 803, Waltham, MA 02254-0803.

#BXNBYJG******** 5-DIGIT 53706
#D0530158/48 123093 072293 AE 69
UW SCH PHARM
LIB
425 N CHARTER ST
MADISON WI 53706-1515

378-7

A COMPARISON OF DIRECTIONAL ATHERECTOMY WITH BALLOON ANGIOPLASTY FOR LESIONS OF THE LEFT ANTERIOR DESCENDING CORONARY ARTERY

ARTAN G. ABELMAN, M.D., ERIC A. COHEN, M.D., BRIAN F. KIMBALL, M.D., RAOUL BONAN, M.D., DONALD R. RIGG, M.D., JOHN G. WEBB, M.D., LOUISE LABARRE, M.D., GERALD BARBEAU, M.D., MOUHIEDDIN TRABOULSI, M.D., BRIAN N. CORBETT, M.D., LEONARD SCHWARTZ, M.D., AND ALEXANDER G. LOGAN, M.D.

Abstract *Background.* Restenosis is a major limitation of coronary angioplasty. Directional coronary atherectomy was developed with the expectation that it would provide better results than angioplasty, including a lower rate of restenosis. We undertook a randomized, multicenter trial to compare the rates of restenosis for atherectomy and angioplasty when used to treat lesions of the proximal left anterior descending coronary artery.

Methods. Of 274 patients referred for first-time, nonsurgical revascularization of lesions of the proximal left anterior descending coronary artery, 138 were randomly assigned to undergo atherectomy and 136 to undergo angioplasty; 257 of 285 eligible patients (97 percent) underwent follow-up angiography at a median of 5.9 months. Computer-assisted quantitative measurements of luminal dimensions were determined from the angiograms obtained before and immediately after the procedure and at follow-up. The primary end point of restenosis was defined as stenosis of more than 50 percent of the vessel's diameter at follow-up.

Results. Quantitative analysis showed that the procedural success rate was higher in patients who underwent atherectomy than in those who had angioplasty (94 percent vs. 88 percent, $P = 0.081$); there was no significant difference in the frequency of major in-hospital complications (5 percent vs. 6 percent). At follow-up, the rate of restenosis was 46 percent after atherectomy and 43 percent after angioplasty ($P = 0.71$). Despite a larger initial gain in the minimal luminal diameter with atherectomy (mean ±SD), 1.45±0.47 vs. 1.16±0.44 mm; $P<0.001$), there was a larger late loss (0.79±0.61 vs. 0.47±0.64 mm, $P<0.001$), resulting in a similar minimal luminal diameter in the two groups at follow-up (1.55±0.60 vs. 1.61±0.66, $P = 0.44$). The clinical outcomes at six months were not significantly different between the two groups.

Conclusions. The role of atherectomy in percutaneous coronary revascularization remains to be fully defined. However, as compared with angioplasty, atherectomy did not result in better late angiographic or clinical outcomes in patients with lesions of the proximal left anterior descending coronary artery. (N Engl J Med 1993;329:228-33.)

IN the past decade percutaneous transluminal coronary angioplasty has been applied to increasingly complex clinical and anatomical situations, with simultaneous improvement in success rates and reduction in complication rates.[1] Despite intensive investigation, however, the incidence of the most common adverse event — restenosis — has remained unacceptably high.[2-6] The substantial clinical and economic impact of restenosis has been a major impetus for the development of alternative percutaneous techniques for coronary revascularization. The directional coronary-atherectomy catheter pioneered by Simpson[7] was the first "non-balloon" device approved for the treatment of coronary artery disease in North America. Although many atherectomy procedures have been performed with this catheter,[8-12] no controlled comparison with conventional balloon angioplasty was carried out before regulatory approval. Our study, the Canadian Coronary Atherectomy Trial, was a randomized, multicenter assessment of the outcomes of these procedures when used for the initial revascularization of lesions of the proximal left anterior descending coronary artery. The primary objective was to determine whether the rate of restenosis, measured by means of quantitative coronary angiography, would be improved by atherectomy.

From Mount Sinai Hospital, Toronto (A.G.A., A.G.L.); Sunnybrook Health Science Centre, Toronto (E.A.C.); Toronto Hospital, Toronto (B.F.K., L.S.); Institut de Cardiologie de Montréal, Montreal (R.B.); Vancouver General Hospital, Vancouver, B.C. (D.R.R.); St. Paul's Hospital, Vancouver (J.G.W.); Ottawa Heart Institute, Ottawa, Ont. (L.L.); Institut de Cardiologie, Hôpital Laval, Quebec, Que. (G.B.); Foothills Hospital, Calgary, Alta. (M.T.); and New Brunswick Heart Centre, St. John, N.B. (B.N.C.) — all in Canada. Address reprint requests to Dr. Abelman at the Cardio-Vascular Clinical Research Laboratory, Mount Sinai Hospital, 1309-600 University Ave., Toronto, ON M5G 1X5, Canada.

Supported by a grant from the Medical Research Council of Canada and by Devices for Vascular Intervention, Redwood City, Calif., and Advanced Cardiovascular Systems, Temecula, Calif.

METHODS

Participating Centers and Investigators

The coordinating center and angiographic core laboratory were at Mount Sinai Hospital, Toronto. All interventional cardiology centers in Canada performing more than 350 coronary angioplasties annually were invited to participate. All investigators had at least two years of experience with angioplasty and had used the Simpson atherectomy device for at least four months for 20 or more procedures, with a success rate exceeding 80 percent and a complication rate below 10 percent. All study procedures were carried out by the investigators at the nine participating centers listed in the Appendix. The study was approved by the institutional review board at each site.

Patient Selection, Recruitment, and Randomization

Prospective subjects for the trial were identified at the time of referral for percutaneous revascularization; decisions regarding eligibility were made by the local investigators on the basis of visual analysis of the diagnostic angiogram. Eligible patients included those with angina or objective evidence of myocardial ischemia and a stenosis of 70–90 percent of the vessel's diameter in the proximal third of the left anterior descending coronary artery that was suitable for either atherectomy or angioplasty. Patients with restenosed lesions were not considered in this study. Specific angiographic exclusion criteria related to the characteristics of the lesion (length of >15 mm; involvement of the ostium or of a branch vessel measuring >2.5 mm in diameter) and the vessel (total occlusion; size of <2.5 mm; heavy calcification or severe tortuosity) or stenosis of the left main coronary artery exceeding 25 percent). Patients with acute myocardial infarction (within one week of the procedure), severe left ventricular dysfunction, or cardiogenic shock were excluded. In

addition, patients with medical conditions likely to preclude follow-up angiography (such as renal insufficiency), those participating in a concurrent study, and those unable to give informed consent were not enrolled.

A log was kept of all eligible, nonenrolled patients at each site. In addition, a registry was maintained documenting the angiographic and clinical reasons for excluding patients undergoing dilation of stenoses of the left anterior descending coronary artery. All atherectomy procedures at participating sites were recorded during the study. Randomization, stratified according to center with a block design, was carried out by means of sealed envelopes in the catheterization laboratory after the initial set of angiograms was obtained. The actual treatment assignments were cross-checked against the computer-generated randomization sequence.

Angiographic Protocol

Because of recognizable differences in the guiding catheters used for atherectomy and angioplasty, angiograms performed before and immediately after the procedures were obtained with 7-French or 8-French diagnostic catheters to ensure that the selection of frames for quantitative coronary analysis would be blinded. At least two orthogonal views of the target lesion were obtained, including the view demonstrating the most severe stenosis. The obliquity and angulation of each view were recorded for later duplication in the post-procedure and follow-up angiograms. The distal 15 cm of the diagnostic catheter was sterilized and retained for measurement. If multiple stenoses were to be dilated, the lesion that was the focus of this study was dilated first. The first three study angiograms from each site were reviewed by the angiographic core laboratory to monitor adherence to the protocol.

Atherectomy and Angioplasty

All the patients received aspirin, a calcium-channel blocker, and nitrates beginning at least 12 hours before the procedure and continuing for 24 hours afterward. Intracoronary nitroglycerin (100 to 200 μg) was injected just before angiography, both before and after the procedure and at follow-up. Heparin was given after the sheath was inserted and was repeated as necessary in doses sufficient to maintain an activated clotting time of more than 300 seconds.

For patients undergoing atherectomy, the introducer sheath was changed to accommodate either a 10-French or an 11-French guiding catheter. Balloon dilation to facilitate atherectomy was discouraged, but if required it was limited to a balloon ≤2.0 mm in size, inflated to no more than 6 atmospheres of pressure. The SCA-1 catheter (Devices for Vascular Intervention, Redwood City, Calif.) was used throughout the trial. The use of the 5-French size, though not prohibited, was strongly discouraged. A minimum of five passes of the cutter across the lesion was recommended during the first insertion of the device; the operators were encouraged to perform additional passes of the cutter and further insertions as required, in an attempt to achieve a final lesion diameter as close to the normal size of the vessel as possible. If balloon angioplasty was selected, any approved balloon-dilation system could be used. Perfusion balloons were permitted either as a primary or a rescue device. The balloon size and the inflation protocols were chosen by the operator to achieve optimal angiographic results.

Operators were encouraged to use only the technique selected by randomization, although crossover was permitted if this did not yield an adequate result. The timing of sheath removal and the dosage and duration of heparin treatment after the procedure were at the discretion of the operator. The patients were hospitalized for at least 18 hours after the procedure.

Follow-up

After the patients were discharged from the hospital, their referring physicians were responsible for routine clinical follow-up. Antianginal medications were discontinued unless specifically indicated. The use of ω-3 fatty acids was prohibited; the use of all other medications was at the discretion of the treating physicians. The local study nurse contacted each patient by telephone every month for six months to ascertain clinical status. Angiography was repeated as close to six months after the procedure as possible, although a range of four to seven months was allowed for logistic reasons. Angiography was allowed before four months had elapsed on the basis of symptoms or the results of noninvasive tests, although if restenosis was not found, a subsequent angiogram was required in the four-to-seven-month period. All follow-up angiograms were performed in the same catheterization laboratory as the original procedure, according to the angiographic protocol described above.

Quantitative Coronary Analysis

Quantitative coronary analysis was carried out in a predetermined order at the coordinating center by investigators who had no knowledge of the specific intervention. In order to avoid any influence of the technique used or the procedural outcome on the analysis, the angiograms obtained before the procedure were analyzed first, those obtained at follow-up were analyzed second, and those obtained after the procedure were analyzed last. With the use of a Tagarno cine projector (Tagarno of America, Dover, Del.) optimal preprocedure, post-procedure, and follow-up frames were selected by a single investigator from identical radiographic projections that best demonstrated the maximal severity and anatomical features of the lesions. Motion artifacts were avoided by selecting frames at end-diastole and excluding those with overlapping branch vessels. All measurements of coronary stenosis were generated with the Cardiac Measurement System (Medical Imaging Systems, Nuenen, the Netherlands) by a single trained research technician. The untapered section of the tip of the diagnostic catheter was used for absolute calibration after individual measurements (in micrometers) of the external diameter had been obtained. The coronary segment of interest was identified by the operator. An interactive, automated edge-detection system outlined the coronary lumen and measured the absolute minimal and reference diameters, the latter derived by a mathematical interpolation function. Validation studies on this system by the trial personnel demonstrated an intraobserver variability of 0.07 mm on immediate reanalysis and of 0.20 mm on 25 paired angiograms analyzed six months apart.

Outcome Assessment

The determination of all angiographic outcomes was based on quantitative measurements made at the angiographic core laboratory. However, eligibility for enrollment was determined by visual assessment of the angiogram at the participating sites. Angiographic success was defined as stenosis of <50 percent after the procedure. Procedural success was defined as the occurrence of angiographic success without a major complication (death, myocardial infarction [new diagnostic Q waves or an increase in the serum creatine kinase level to two times the local normal value], or coronary artery bypass surgery) during the index hospitalization. Electrocardiograms and enzyme levels were reviewed by an experienced cardiologist who had no knowledge of the technique used or the angiographic outcome. Other adverse events included abrupt vessel closure and injury to the vascular access site requiring transfusion or surgery). Major complications were reviewed on an ongoing basis by an independent safety monitor. As a dichotomous variable, restenosis was defined as stenosis of more than 50 percent at follow-up. Luminal dimensions were also examined as continuous data.

Statistical Analysis

The prespecified primary analysis of angiographic and procedural outcomes followed the intention-to-treat principle. Categorical data were compared with continuity-adjusted or exact chi-square statistics as appropriate, and continuous data with analysis-of-variance techniques. Confidence intervals for the observed restenosis rates and their differences were calculated with the normal approximation. Logistic regression was used to identify variables contributing to restenosis from among those known before the procedure. In addition to the randomization assignment, the variables considered included [illegible], sex, symptom status [illegible], unstable angina), and all two-way interactions. Because the effects of atherectomy and angioplasty on restenosis are not independent of their

effects on immediate procedural outcomes, all the patients who underwent follow-up angiography were included in the primary analysis. However, patients with stenosis exceeding 50 percent after the procedure were excluded in a secondary analysis. Continuous data are given as means ±SD; categorical data are presented as rates, with 95 percent confidence intervals. Differences between the groups were considered significant if the P value was less than 0.05 for a two-tailed test.

Results

Characteristics of the Patients

Between July 1991 and August 1992, 274 patients were selected for the study: 138 were randomly assigned to undergo atherectomy and 136 to undergo angioplasty. Two of the randomization envelopes (at separate sites) were inadvertently used out of sequence, but this did not affect the overall treatment allocation. The 274 procedures constituted 7 percent of all coronary interventions and 16 percent of procedures performed on the left anterior descending coronary artery at participating sites during this period. Fifty-eight percent of all atherectomy procedures performed at the study centers were included in the trial. Of 4024 patients screened, 1718 had lesions of the left anterior descending coronary artery, of these patients, 61 percent had angiographic and 12 percent clinical reasons for exclusion. Among the patients who were angiographically and clinically eligible, 93 percent were randomized, 3 percent were already participating in another trial, and 3 percent declined to be enrolled (the reasons for exclusion were unknown in 1 percent).

The base-line characteristics of the patients are shown in Table 1. The patients randomly assigned to undergo atherectomy were more likely to be female and were slightly older, whereas the angioplasty group had a higher proportion of patients with unstable angina. Other clinical and angiographic characteristics were reasonably well matched. Age and sex were highly correlated and probably represent a single imbalance in the base-line characteristics. After quantitative analysis, eight patients (three in the atherectomy group and five in the angioplasty group) were found to have had stenosis of less than 50 percent (mean [±SD], 46±5 percent) before the procedure; the visually estimated stenoses for these patients ranged from 60 to 95 percent.

Table 1. Base-Line Clinical and Angiographic Characteristics of Patients Randomly Assigned to Undergo Atherectomy or Angioplasty.*

Characteristic	Atherectomy (N = 138)	Angioplasty (N = 136)
Male sex (%)	66	87
Age (yr)	57.7±10.2	54.6±10.0
Coronary risk factor (%)		
Diabetes	17	15
Hypertension	28	25
Hypercholesterolemia	46	43
Current smoker	28	26
Unstable angina (%)	39	52
Previous myocardial infarction (%)	36	37
Within 1 mo of study (%)	9	9
Left ventricular ejection fraction <35% (%)	6	9
Multivessel disease (%)	27	26
Morphology of lesion† (%)		
ARA segment		
12	60	71
13	40	29
TIMI flow grade		
2	36	19
3	64	89
ACC or ARA lesion type		
A	37	13
B1	43	50
B2	20	36
Calcification		
Mild	48	59
Moderate	18	10
Moderate tortuosity	20	15
Lesion angulation >45 degrees	23	13
Thrombus	17	15

*Plus-minus values are means ±SD. Because of rounding, not all values sum to 100 percent. ARA denotes American Heart Association, TIMI Thrombolysis in Myocardial Infarction study, and ACC American College of Cardiology.

Procedural Outcomes

Atherectomy was attempted and abandoned in 15 of the 138 patients randomly assigned to undergo this procedure (11 percent) because of guiding-catheter problems in 5 and an inability to cross the lesion in 10, despite balloon dilation before the procedure in 4 of the 10. In four other patients, dilation before the procedure successfully facilitated atherectomy. An additional 11 patients (8 percent) required adjunctive balloon dilation after atherectomy. In the group randomly assigned to undergo angioplasty, 5 of the 136 patients (4 percent) were crossed over to an alternative technique — 3 underwent atherectomy and 2 received intracoronary stents. Tissue was retrieved from all the patients who underwent atherectomy except the 15 in whom the procedure was abandoned.

Procedural outcomes and the complications that occurred during hospitalization are shown in Table 2. Quantitative analysis revealed that angiographic success was achieved in 125 of 138 patients undergoing atherectomy (90 percent) and 124 of 136 patients undergoing angioplasty (91 percent) (P = 0.917); the procedural success rates were 94 percent and 88 percent, respectively (P = 0.061). There were no in-hospital deaths and only one Q-wave myocardial infarction. The incidence of other major complications, including in-hospital coronary bypass surgery and non–Q-wave myocardial infarction, was similar in the two groups (composite outcome 9 percent for the atherectomy group and 6 percent for the angioplasty group; P = 0.98). Ninety-one percent of the patients in each group were free of any adverse event during hospitalization.

Details of the procedures and devices used are also shown in Table 2. The duration of the procedure and of fluoroscopy, as well as the amount of radiographic contrast material used, was significantly higher in the

Table 2. Procedural Outcomes, In-Hospital Complications, and the Types of Devices Used in Patients Undergoing Atherectomy or Angioplasty.*

Variable	Atherectomy (N = 136)	Angioplasty (N = 129)	P Value
Procedural outcomes (%)			
Angiographic success			
Visual	99	97	0.36
Quantitative	98	91	0.017
Procedural success	98	85	0.001
In-hospital complications (%)			
Mortality	0	0	0.99
Coronary bypass surgery	1.4	4.4	0.17
Myocardial infarction			
Q wave	0.7	0	0.99
Non–Q wave	3.6	3.7	0.72
Abrupt occlusion	0.7	5.1	0.08
Vascular injury	2.9	1.5	0.69
Freedom from any adverse event	91	91	0.86
Interventional devices used†			
No. of atherectomy catheters used	137	4	—
No. of balloons used	38	172	—
Size of final device‡			
5 French or <3.0 mm	5	8	—
6 French or <3.5 mm	66	50	—
7 French or ≥3.5 mm	29	42	—
Catheterization data			
Length of occlusion (mm)	30.6±22.3	30.3±20.4	0.92
Length of fluoroscopy (min)	22.6±14.1	18.6±10.5	0.02
Amount of radiographic contrast medium (ml)	339±147	253±114	0.001
Heparin use			
Use before procedure (%)	73	81	0.11
Dose during procedure ($U \times 10^{-3}$)	12.1±4.2	12.8±5.6	0.88
Use after procedure (%)	67	66	0.98
Laboratory values			
Change in hemoglobin (g/dl)	−1.17±1.75	−1.19±1.36	0.91
Change in serum creatinine (mg/dl)	0.034±0.24	−0.007±0.20	0.39

*Plus–minus values are means ±SD. Percentages of patients in each group.

†Many patients required more than one device to complete the procedure; the figures give the total number of devices used, including those used after crossover to the alternative technique.

‡The size of the final device used is given as the French size or the size in millimeters, depending on whether the final device was an atherectomy catheter or an angioplasty balloon, respectively.

§The relevant values in conventional units are, multiply by 88.4.

atherectomy group than in the angioplasty group. There was no difference between the groups in the use of heparin, periprocedural changes in hemoglobin or serum creatinine concentrations, or the length of hospitalization after the procedure (1.4 days in each group).

Angiographic Restenosis

Angiography was performed a median of 5.9 months after the procedure in 257 of the 265 patients (97 percent) who had not received a stent or who had not had coronary bypass surgery during the index hospitalization (128 of 136 in the atherectomy group and 129 of 129 in the angioplasty group). Follow-up angiograms were obtained within four months of the interventional procedure in 38 patients, 32 of whom had restenosis according to quantitative angiographic analysis. The remaining six (three in the atherectomy group and three in the angioplasty group) were considered to have restenosis on the basis of visual assessment but were subsequently found to have stenosis of less than 50 percent on quantitative review.

The rate of restenosis was 46 percent in the atherectomy group (95 percent confidence interval, 37 to 54 percent) and 43 percent in the angioplasty group (95 percent confidence interval, 34 to 52 percent) ($P = 0.71$). When the subjects with stenosis of more than 50 percent after the procedure were excluded from the analysis (3 in the atherectomy group and 10 in the angioplasty group), the resulting rates of restenosis were 45 percent in the atherectomy group (95 percent confidence interval, 37 to 54 percent) and 39 percent in the angioplasty group (95 percent confidence interval, 30 to 48 percent) ($P = 0.31$). A separate analysis of the patients who were treated successfully with use of the assigned technique alone also yielded similar results (44 percent for the atherectomy group [110 patients] and 39 percent for the angioplasty group [112 patients], $P = 0.59$).

Stepwise logistic regression revealed that only unstable angina remained as a predictor of restenosis. Among the patients with unstable angina, the rate of restenosis was 49 percent after atherectomy (95 percent confidence interval, 35 to 63 percent) and 49 percent after angioplasty (95 percent confidence interval, 37 to 62 percent); among the patients with stable angina, the rates were 44 percent after atherectomy (95 percent confidence interval, 33 to 55 percent) and 35 percent after angioplasty (95 percent confidence interval, 23 to 49 percent). Despite the differences in the rates of restenosis, there was no significant interaction between angina status and treatment assignment after we controlled for age and sex ($P = 0.29$ for the interaction term). After adjustment for angina status (stable vs. unstable), the rates of restenosis were 46 percent in the atherectomy group and 42 percent in the angioplasty group. These adjusted rates exclude, with 90 percent certainty, a difference in the restenosis rates of more than 7 percent in favor of atherectomy or of more than 15 percent in favor of angioplasty.

The luminal dimensions before and after the procedure and at follow-up are given in Table 3. The mean reference diameters before the procedure were similar in the two groups. The increase in the minimal luminal diameter was greater with atherectomy than with angioplasty (1.45±0.47 vs. 1.16±0.44 mm, $P<0.001$); however, the gain was offset by a greater loss during the follow-up period (0.79±0.61 vs. 0.47±0.64 mm, $P<0.001$). Consequently, there was no significant difference between groups in the minimal luminal diameter at follow-up (1.55±0.60 vs. 1.61±0.68 mm, $P = 0.44$). The cumulative-frequency distributions of the minimal luminal diameters are shown in Figure 1.

Clinical Follow-up

Clinical data were available for all 265 patients eligible for follow-up. There were no significant differences between the two groups with regard to clin-

ical events. One sudden death occurred in a patient who had undergone atherectomy, and there were two myocardial infarctions, both in patients who had undergone angioplasty. Revascularization was repeated in 39 patients (by percutaneous methods in 32 and surgery in 7) in the atherectomy group and 35 patients (by percutaneous methods in 30 and surgery in 6) in the angioplasty group. Seventy-one percent of the patients in each group had no late adverse events. The proportion of patients with Canadian Cardiovascular Society class III or IV angina at any time during the follow-up period was not significantly different between groups (30 percent in the atherectomy group and 20 percent in the angioplasty group, $P = 0.11$).

Discussion

Although there was a higher procedural success rate with atherectomy than with angioplasty in this trial, a comparison of the late angiographic and clinical outcomes of the two techniques disclosed no advantage of atherectomy over angioplasty when used for the initial treatment of lesions in the proximal left anterior descending coronary artery. The angiographic success rate on quantitative analysis was significantly higher with atherectomy (98 percent vs. 91 percent); however, about 10 percent of these "successful" atherectomies resulted from a crossover to conventional balloon angioplasty after atherectomy was abandoned, and another 10 percent required balloon dilation before or after the atherectomy to complete the procedure. In contrast, operators resorted to an alternative technique in fewer than 5 percent of the patients randomly assigned to undergo angioplasty. The rates of adverse events in the hospital were similar in both groups. Procedural results and the incidence of complications with atherectomy in this trial were comparable to or better than those reported in earlier series in the literature.[8-13]

Lesions of the proximal left anterior descending coronary artery have been associated with restenosis rates of 40 to 45 percent after angioplasty.[14,15] Conversely, a post hoc analysis of atherectomy procedures performed in the same anatomical location has suggested a much lower rate (<25 percent).[16] Such lesions are frequently eccentric and bulky — morphologic features generally considered to be less than ideal for angioplasty but suitable for atherectomy. Furthermore, access of the stiffer, higher-profile atherectomy catheter to these lesions is facilitated by their proximity and the relative absence of vessel tortuosity. These considerations formed the rationale for restricting the target lesion in this trial to stenoses of the proximal left anterior descending coronary artery; if atherectomy were superior to angioplasty, it should be most evident for lesions in this location.

Despite this strategy, quantitative analysis of follow-up angiograms in 97 percent of the eligible patients failed to demonstrate a significant difference in the prespecified dichotomous outcome of restenosis. The actual rates of restenosis in both groups in this trial are consistent with those in contemporary reports.[15-18] The rates of the composite clinical outcomes (including death, myocardial infarction, coronary bypass surgery, the need for additional coronary intervention, and recurrence of angina), which are of primary concern to patients and their physicians, were also similar for both procedures. However, atherectomy procedures consumed more catheterization-laboratory resources and subjected patients to more radiation than angioplasty procedures.

As shown by other investigators,[11,12] atherectomy was associated with larger minimal luminal diameters and with less residual stenosis after the procedure than angioplasty. These favorable angiographic features

Table 3. Luminal Dimensions in Patients Who Underwent Atherectomy or Angioplasty.*

Variable	Atherectomy (N = 336)	Angioplasty (N = 338)	P Value
Preprocedure			
Reference value	3.13±0.47	3.25±0.50	0.11
Minimal luminal diameter (mm)	0.89±0.28	0.96±0.31	0.15
Stenosis (%)	71.5±8.6	70.33±9.2	0.61
Postprocedure			
Reference value (mm)	3.15±0.46	3.16±0.47	0.97
Minimal luminal diameter (mm)	2.34±0.44	2.10±0.41	<0.001
Stenosis (%)	25.6±11.2	33.9±11.6	<0.001
At follow-up			
Reference value (mm)	3.03±0.51	3.12±0.48	0.13
Minimal luminal diameter (mm)	1.55±0.66	1.48±0.68	0.34
Stenosis (%)	48.7±18.6	48.4±20.0	0.91
Change in minimal luminal diameter			
Gain (mm)	1.45±0.47	1.16±0.44	<0.001
Loss (mm)	0.78±0.61	0.61±0.60	<0.001
Net gain (mm)	0.66±0.65	0.55±0.61	0.04

*Plus-minus values are means ± SD. Reference values are the average luminal diameters of normal segments. Gain is the difference between the final dilated balloon or postprocedure luminal diameter and the minimal luminal diameter at the follow-up study, and net gain is the difference between the final dilated balloon or postprocedure luminal diameter and the follow-up minimal luminal diameter at the same lesion site.

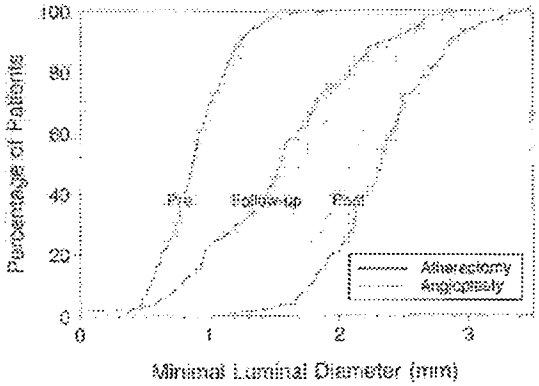


Figure 1. Cumulative-Frequency Distribution Curves Showing the Percentage of Patients with Given Minimal Luminal Diameters before Atherectomy or Angioplasty (Pre), after the Procedure (Post), and at Follow-up.

The preprocedure curves are nearly superimposed, indicating a very similar distribution of minimal luminal diameters among the atherectomy and angioplasty groups. The post-procedure curve for atherectomy lies to the right of the corresponding angioplasty curve, as a result of the larger minimal luminal diameters obtained with atherectomy. At follow-up, the curves come together, demonstrating that this increase was not maintained.

were offset, however, by a proportionally greater deterioration during the follow-up period, so that the net gain in either luminal diameter or percent diameter was virtually the same for both procedures. This is shown by the cumulative-frequency distribution curves of the minimal luminal diameter, which were nearly identical at follow-up. These findings are supported by data from both laboratory and clinical studies demonstrating that the extent of subsequent intimal hyperplasia is proportional to the depth of arterial injury[22] or to the improvement in luminal diameter at the time of the procedure[23,24]; in other words, the greater the gain, the greater the loss. Unresolved is the question of whether the ratio of loss to gain is constant[25,26] or varies according to the device used or the amount gained[18,19]; our data, showing proportionally greater loss after atherectomy, would tend to support the latter possibility.

In addition to compressing and reshaping atheroma, atherectomy excises tissue and debulks plaques; it was anticipated that this mechanism would result in a lower rate of restenosis than that occurring after angioplasty. These expectations were not fulfilled in this trial. Nonetheless, coronary atherectomy is a new technique that continues to evolve. A more aggressive approach to atherectomy that results in larger luminal diameters has recently been advocated by some investigators.[24-26] Whether this would have resulted in lower rates of restenosis without a concurrent increase in complications cannot be determined from our study. The role of atherectomy in dealing with restenosed lesions or specific anatomical situations considered unfavorable for angioplasty, such as ostial, bifurcated, or bypass-graft lesions, is still being assessed. Furthermore, it is conceivable that its application in vessels other than the left anterior descending coronary artery, future enhancements in its design, or greater operator experience in its use may yet affect restenosis. However, the similar rates of restenosis and the similar luminal dimensions found at follow-up after atherectomy or angioplasty in this trial may well represent an inevitable consequence of the vascular response to intervention.

Appendix

The following institutions, investigators, and staff members participated in the Canadian Coronary Atherectomy Trial or acted as advisers: *Participating centers and investigators* — Toronto Hospital, Toronto: A.G. Adelman, B.P. Kimball, and J. Richards; Institut de Cardiologie de Montréal, Montreal: R. Bonan and G. Renaud; Vancouver General Hospital, Vancouver: D.R. Ricci, C. Buller, C. Dupuis, and S. McCarthy; St. Paul's Hospital, Vancouver: J.G. Webb, R. Carere, and D. Hemrick; Ottawa Heart Institute, Ottawa: L. Laramée, J.F. Marquis, and B. Dowell; Institut de Cardiologie, Hôpital Laval, Quebec: G. Barbeau and M.M. Larivière; Foothills Hospital, Calgary: M. Traboulsi, D. Galbraith, K. Hildebrand, and D. Hasman; New Brunswick Heart Centre, St. John: S.N. Corbett and J. Creighton; and Sunnybrook Health Science Centre, Toronto: E.A. Cohen, S. Naqvi, S. Dehaan, and N. Cooper. *Trial advisers* — Mount Sinai Hospital, Toronto: A. Logan (Clinical Epidemiology); Toronto Hospital, Toronto: L. Schwartz (Clinical Events Adjudication), W. Mahon (Clinical Trials), and P. Liu and A. Gotlieb (Tissue Pathology); Institut de Cardiologie de Montréal, Montreal: J. Lespérance (Quantitative Coronary Analysis); and Royal Columbian Hospital, New Westminster, B.C.: M. Henderson (Safety Monitoring). *Coordinating center and core laboratory staff* — Mount Sinai Hospital, Toronto: F. Slaughter (Study Coordinator), K. Sykora (Study Biostatistician), S. Bui (Quantitative Coronary Analysis Technician), J. King, C. Ellis, K. Kwok, Y. Wu, M. Landry, and C. Prasad.

References

1. Detre K, Holubkov R, Kelsey S, et al. Percutaneous transluminal coronary angioplasty in 1985–1986 and 1977–1981. N Engl J Med 1988;318:265-70.
2. Nobuyoshi M, Kimura T, Nosaka H, et al. Restenosis after successful percutaneous transluminal coronary angioplasty: serial angiographic follow-up of 229 patients. J Am Coll Cardiol 1988;12:616-23.
3. Beatt KJ, Serruys PW, Hugenholtz PG. Restenosis after coronary angioplasty: new standards for clinical studies. J Am Coll Cardiol 1990;15:491-8.
4. Bourassa MG, Lespérance J, Eastwood C, et al. Clinical, physiologic, anatomic and procedural factors predictive of restenosis after percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1991;18:368-76.
5. Popma JJ, Califf RM, Topol EJ. Clinical trials of restenosis after coronary angioplasty. Circulation 1991;84:1426-36.
6. Rensing BJ, Hermans WRM, Deckers JW, de Feyter PJ, Tijssen JGP, Serruys PW. Lumen narrowing after percutaneous transluminal coronary balloon angioplasty follows a near gaussian distribution: a quantitative angiographic study in 1,445 successfully dilated lesions. J Am Coll Cardiol 1992;19:939-45.
7. Hinohara T, Selmon MR, Robertson GC, Braden L, Simpson JB. Directional atherectomy: new approaches for treatment of obstructive coronary and peripheral vascular disease. Circulation 1990;81:Suppl IV:IV-79–IV-91.
8. Serruys PW, Umans VAWM, Strauss BH, et al. Quantitative angiography after directional coronary atherectomy. Br Heart J 1991;66:122-9.
9. Ellis SG, De Cesare NB, Pinkerton CA, et al. Relation of stenosis morphology and clinical presentation to the procedural results of directional coronary atherectomy. Circulation 1991;84:644-53.
10. Popma JJ, Topol EJ, Hinohara T, et al. Abrupt vessel closure after directional coronary atherectomy. J Am Coll Cardiol 1992;19:1372-9.
11. Adelman AG, Cohen EA, Carere RG, Kimball BP. Directional coronary atherectomy at the Toronto and Mount Sinai Hospitals: report of the initial 120 procedures. Can J Cardiol 1992;8:702-8.
12. Hinohara T, Robertson GC, Selmon MR, et al. Restenosis after directional coronary atherectomy. J Am Coll Cardiol 1992;20:623-32.
13. Fishman RF, Kuntz RE, Carrozza JP Jr, et al. Long-term results of directional coronary atherectomy: predictors of restenosis. J Am Coll Cardiol 1992;20:1101-10.
14. Hirshfeld JW Jr, Schwartz JS, Jugo R, et al. Restenosis after coronary angioplasty: a multivariate statistical model to relate lesion and procedure variables to restenosis. J Am Coll Cardiol 1991;18:647-56.
15. Frierson JH, Dimas AP, Whitlow PL, et al. Angioplasty of the proximal left anterior descending coronary artery: initial success and long-term follow-up. J Am Coll Cardiol 1992;19:745-51.
16. Simpson JB, Rowe MH, Selmon MR, et al. Restenosis following directional coronary atherectomy in de novo lesions of native coronary arteries. Circulation 1990;82:Suppl III:III-313. abstract.
17. Popma JJ, De Cesare NB, Ellis SG, et al. Clinical, angiographic and procedural correlates of quantitative coronary dimensions after directional coronary atherectomy. J Am Coll Cardiol 1991;18:1183-9.
18. Umans VA, Strauss BH, de Feyter PJ, Serruys PW. Edge detection versus videodensitometry for quantitative angiographic assessment of directional coronary atherectomy. Am J Cardiol 1991;68:534-9.
19. Serruys PW, Foley DP, de Feyter PJ. Restenosis after coronary angioplasty: a proposal of new comparative approaches based on quantitative angiography. Br Heart J 1992;68:417-24.
20. Kimball BP, Bui S, Cohen EA, Carere RG, Adelman AG. Acute outcome of directional coronary atherectomy vs standard balloon angioplasty in de novo left anterior descending stenoses. Chest 1993;104:816-22.
21. Kimball BP, Bui S, Cohen EA, Carere RG, Adelman AG. Comparison of acute elastic recoil after directional coronary atherectomy versus standard balloon angioplasty. Am Heart J 1992;124:1459-66.
22. Schwartz RS, Huber KC, Murphy JG, et al. Restenosis and the proportional neointimal response to coronary artery injury: results in a porcine model. J Am Coll Cardiol 1992;19:267-74.
23. Beatt KJ, Serruys PW, Luijten HE, et al. Restenosis after coronary angioplasty: the paradox of increased lumen diameter and restenosis. J Am Coll Cardiol 1992;19:258-66.
24. Kuntz RE, Hinohara T, Safian RD, Selmon MR, Simpson JB, Baim DS. Restenosis after directional coronary atherectomy: effects of luminal diameter and deep wall excision. Circulation 1992;86:1394-9.
25. Kuntz RE, Safian RD, Carrozza JP, Fishman RF, Mansour M, Baim DS. The importance of acute luminal diameter in determining restenosis after coronary atherectomy or stenting. Circulation 1992;86:1827-35.
26. Kuntz RE, Gibson CM, Nobuyoshi M, Baim DS. Generalized model of restenosis after conventional balloon angioplasty, stenting and directional atherectomy. J Am Coll Cardiol 1993;21:15-25.

American Heart Association Top 10 Advances for 2003

AHA News 12/31/2003

American Heart Association's top 10 advances for 2003 include new blood pressure guidelines, novel blood thinners

DALLAS, Dec. 31 – Novel drugs for heart failure, new blood pressure treatment guidelines and the success of a public access defibrillation program are among the top 10 advances in heart disease and stroke for 2003, said Augustus O. Grant, M.D., Ph.D., president of the American Heart Association.

Other major milestones include a new blood thinner, a potent clot-busting substance extracted from the saliva of vampire bats, and a new approach to clear plaque from arteries.

Created in 1996, the "Top 10" list highlights major gains in heart disease and stroke research. The top 10 for 2003 include:

1. New high blood pressure guidelines create new at-risk classification. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII) said "prehypertension" is a new classification that includes people with blood pressures between 120-39 millimeters of mercury (mm Hg) systolic (the top number in a blood pressure reading) and 80-89 mmHg diastolic (bottom number). Prehypertension is an ominous precursor to chronic high blood pressure, according to new guidelines released in 2003 by the federal government.

Lifestyle changes such as eating a healthy diet, exercising regularly and quitting smoking, can help to prevent, or at least postpone, the development of full-blown hypertension in patients with prehypertension. This may also reduce their risk of later developing heart disease, stroke and kidney disease, the guidelines state.

The guidelines also state that in people over age 50, systolic pressure greater than140mmHg is a more important cardiovascular disease risk factor than diastolic blood pressure. Therefore, people with a systolic pressure of 140 mm Hg or greater in that age group should be treated regardless of the diastolic blood pressure level.

Also, the guidelines suggest most hypertensive patients will require two or more antihypertensive medications to achieve goal blood pressure (less than 140/90 mm Hg, or less than 130/80 mm Hg for those with diabetes or chronic kidney disease).

High blood pressure (hypertension) affects about 50 million Americans and 1 billion people worldwide.

Citation: *JAMA Express*, June 14, 2003.

2. New blood thinner offers first potential alternative in 50 years. This year saw the introduction of a new, easier to manage blood thinner pill - and the first potential alternative in 50 years to warfarin, the standard treatment given to millions of people to prevent blood clots.

In the Stroke Prevention Using the Oral Direct Thrombin Inhibitor Ximelagatran In Patients with Nonvalvular Atrial Fibrillation (SPORTIF V) trial, anticoagulation with warfarin, which reduces the risk of ischemic stroke and other systemic and embolic events in patients with atrial fibrillation (AF), was compared with the oral direct thrombin inhibitor ximelagatran. Patients with AF and at least one stroke risk factor (3,922 individuals) were randomized to receive adjusted-dose warfarin or fixed-dose oral ximelagatran. The primary endpoint was all strokes (ischemic and hemorrhagic) and systemic embolic events. Primary event rates were 1.2 percent/year in the warfarin group and 1.6 percent/year in the ximelagatran group, not a significant difference. When all-cause mortality was included with the primary events, the rate difference between groups by ITT was even less, at 0.10 percent/year. Rates of disabling or fatal stroke, hemorrhagic stroke and major bleeding did not differ significantly between groups, but combined minor and major bleeding was lower with ximelagatran (47 percent/year versus 37 percent/year). In this large, double-blind trial involving high-risk patients with AF, fixed-dose, oral ximelagatran was at least as effective as well-controlled warfarin for preventing stroke and systemic embolic events. It also resulted in less bleeding, confirming the results of the SPORTIF III open-label trial.

A second study found that ximelagatran may be more effective than warfarin in preventing blood clots after knee replacement surgery. In that study, 2,301 patients in five countries received low or high dose ximelagatran or warfarin for up to 12 days after surgery. Of these 2301 patients, 1,851 were included n the analysis of drug efficacy. Twenty percent of patients in the high-dose ximelagatran group developed clots or died, compared with 25 percent in the lower-dose group and 28 percent in the warfarin group.

Ximelagatran was developed as an alternative to warfarin in an effort to find a drug that was easier for patients and doctors to manage. While widely prescribed after strokes, heart attacks and knee surgery, warfarin requires close laboratory monitoring for dose adjustment, and interacts with certain foods and drugs. Studies show ximelagatran does not require adjustments or close monitoring, and has no food or drug interactions.

Citation: American Heart Association Scientific Sessions 2003.

***The New England Journal of Medicine,* Oct. 29, 2003.**

3. Public defibrillators and trained volunteers are a lifesaver for cardiac arrest victims. Training volunteers to use automated external defibrillators (AEDs) distributed in shopping malls, sports venues and other

high traffic public places can double the odds that cardiac arrest victims will survive, researchers reported at the American Heart Association's Scientific Sessions 2003 in Orlando, Fla.

Each year, an estimated 400,000 to 460,000 Americans die of heart disease in an emergency room or before reaching a hospital. Paramedics and firefighters are trained to use defibrillators to shock victims' hearts back to normal – if they arrive in time. But with only a 5-10 minute window of opportunity, most do not arrive in time.

The new study was designed to see if having AEDs available in public places for use by trained volunteers could improve the chance for survival. For the study, AEDs were placed in key locations at nearly 1,000 shopping centers, recreation centers, apartment complexes, entertainment complexes and community centers in 24 cities across the United States and Canada. The researchers then enlisted about 20,000 volunteers. All were taught to do cardiopulmonary resuscitation; half were also taught how to use the AEDs. Over the next 21.5 months, the volunteers attempted to resuscitate nearly 300 cardiac arrest victims. Forty-four survived, 29 of whom were treated by the volunteers who used the AEDs plus CPR and 15 of whom were treated by those who did CPR alone.

The results are so encouraging that they are expected to jumpstart efforts to get more AEDs in public places and train additional volunteers.

Citation: American Heart Association Scientific Sessions 2003, Plenary Session III, Late-Breaking Clinical Trials, Presented Nov. 11, 2003.

4. New treatment option for heart failure patients. People whose hearts have been weakened or damaged by a heart attack got a much needed new treatment option in October, when the U.S. Food and Drug Administration approved epleronone, a member of a class of drugs known as aldosterone blockers, for the treatment of congestive heart failure following a heart attack.

The approval was based in large part on the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), released in April.

The study of 6,632 patients showed that those who took eplerenone on top of standard congestive heart failure treatment were 15 percent less likely to die from any cause, 17 percent less likely to die from heart disease, and 13 percent less likely to die of heart disease or be hospitalized, compared with those who took placebo plus standard therapy. Standard treatment for congestive heart failure after a heart attack includes heart surgery, ACE inhibitors, aspirin, beta blockers and statins, according to the study authors.

More than a million Americans have a heart attack annually and about half (515,000) die. More than a third of heart attack survivors will develop heart failure, half of whom will die within five years. Epleronone blocks the actions of the hormone aldosterone in the body. High levels of aldosterone, which causes the kidneys to retain salt and water, are associated with increased risks in congestive heart failure patients.

Citation: ***The New England Journal of Medicine,*** **April 3, 2003.**

5. Heal thyself: Patients' bone marrow cells restore failing hearts. Bone marrow cells taken from patients' own blood healed heart muscle that was damaged during a heart attack, providing a new treatment for failing hearts, researchers reported at the American Heart Association's Scientific Sessions 2003 in Orlando, Fla. The bone marrow cells, which doctors infused directly into the patients' ailing hearts, fueled new heart cell growth, which strengthened the heart's pumping capacity. German researchers studied 40 heart attack patients in whom blood vessels had been treated with balloon angioplasty and into which a mesh tube called a stent had been placed to help keep it open. Twenty patients received the bone marrow stem cells; 20 others who declined the experimental procedure comprised the control group. A few days after the patients' heart attacks, doctors obtained bone marrow cells from members of the treatment group. The cells were implanted into the damaged muscle, using a catheter threaded into a heart artery. Three months later, the stem cell patients had less heart muscle damage and an increased ejection fraction, a measure of the heart's pumping ability. Other research teams are also investigating the use of stem cells harvested from bone marrow to reverse the muscle damage caused by a heart attack or to strengthen hearts that have been severely weakened over the years by congestive heart failure. Stem cells are immature cells that still can transform, or differentiate, into different types of cells, such as heart muscle and blood vessels. While the work is still early, it could eventually revolutionize the treatment of heart disease, researchers say.

Citation: American Heart Association Scientific Sessions 2003, Abstract P1929, Presented Nov. 10, 2003.

6. Drug-coated stents effective in "real world" patients. Drug-coated stents –which the American Heart Association in 2001 picked as one of the biggest potential breakthroughs in treating cardiovascular disease – are starting to live up to their promise, with researchers reporting in 2003 that the devices are safe and effective at preventing death, heart attack or repeat procedures in "real world" patients. People in the real world are often sicker or older than those selected for clinical trials.

One-year results from the Rampamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry of 958 patients with previously untreated blocked arteries show that 9.7 percent of patients who received sirolimus-eluting Cypher stents had a major adverse cardiac event, compared with 14.8 percent of those who received bare stents. Only 3.7 percent of the patients treated with drug-eluting stents had a renarrowing of the treated vessel that required repeat procedures, while 10.9 percent of the patients in the bare stent group required repeat interventions.

Citation: Rapid access issue of *Circulation: Journal of the American Heart Association*. December 23, 2003.

7. Newly mapped gene for ruptured heart may lead to life-saving treatment. Researchers studying an inherited life-threatening heart disorder reported in 2003 that they had mapped a new location for a genetic mutation that causes the problem. The finding may lead to early, life-saving treatment for familial thoracic aortic aneurysm and dissection (TAAD), in which the aorta enlarges until it eventually bursts or dissects.

The aorta is the large artery that receives oxygen-rich blood from the heart. Arteries that branch from the aorta distribute blood to the rest of the body.

Currently people with TAAD are unaware of the risk they face because the slowly enlarging aorta does not cause any symptoms until it has reached a critical diameter. At that point, the aorta dissects or ruptures, both of which are life-threatening.

So researchers have been searching all the human genes to identify the genes responsible for TAAD. But they first needed to identify the chromosome sites of the genes. The team had already identified two chromosome sites: 5q13-15 (*TAAD1*) and 11q23.2-q24 (*FAA1[familial aortic aneurysm]*) – but some families had disease that could not be linked to these sites. In the new study, researchers examined four generations of one family of Swiss-German heritage which had a history of TAAD unlinked to the previously identified chromosome locations. Researchers collected and analyzed DNA samples from 52 family (from a fourth generation family) members and identified a new location for familial TAAD at 3p24-25. They named it *TAAD2.*

As researchers continue to search for other chromosome sites, they are also trying to pinpoint the exact mutant gene. Once the mutation is identified, researchers may develop tests to identify people who are at risk for familial TAAD. Then these high-risk people can be closely monitored so that they can undergo surgery to correct the disorder before the aorta is at risk for dissection.

Citation: Rapid access issue of *Circulation: Journal of the American Heart Association*, June 24, 2003.

8. Vampire bats yield potent clot buster. A clot-busting substance extracted from the saliva of vampire bats may significantly increase the number of ischemic stroke victims eligible for clot-busting treatment, Australian researchers reported in 2003.

That's because the clot buster, called *Desmodus rotundus* salivary plasminogen activator (DSPA), or desmoteplase, may be able to be used up to three times longer than the current stroke treatment window – without increasing the risk for additional brain damage. The vampire bat saliva-derived DSPA targets and destroys fibrin, the structural scaffold of blood clots, said Monash University researchers.

Ischemic strokes are caused when a blood clot or series of clots block blood supply to the brain. The only Food and Drug Administration-approved clot buster for treating ischemic stroke is intravenous tissue

plasminogen activator, (rt-PA). However, rt-PA is administered to only a small percentage of patients because current protocols allow treatment only within three hours of stroke onset. Also, rt-PA has been shown to promote brain cell death in some animal studies.

Although most of the experiments with DSPA have been limited to animal studies, the novel clot buster is now being tested up to nine hours after stroke onset in a European study of human stroke patients. The DSPA agent is also being tested currently in the United States.

Citation: Rapid access issue of *Stroke: Journal of the American Heart Association.* Jan. 10, 2003.

9. A shot of good cholesterol may clear out blocked arteries. An experimental treatment that seems to reverse coronary artery disease made headlines in 2003, when Cleveland Clinic researchers reported that just five weeks of weekly infusions of a synthetic form of high-density lipoprotein, or HDL, cholesterol can remove significant amounts of plaque from fat-clogged arteries.

In the study, 57 patients with acute coronary syndromes defined as unstable angina, non-ST-or ST elevation myocardial infarction were randomly assigned to treatment with a synthetic version of HDL known as apolipoprotein Milano AI/phospholipid complexes (ETC-216) or control groups. They were given intravenously once a week. A total of 47 patients completed the study, 11 in the placebo group and 21 in the low-dose and 15 in the high-ETC 216 groups. The synthetic substance mimics a naturally occurring genetic variation found in a small group of people living in northern Italy that appears to protect against atherosclerosis. As determined by intravascular ultrasound at baseline and six weeks after treatment, the volume of fatty deposits in the arteries (atheroma) decreased by an average of 1.06 percent in the combined group that got the ETC-216 infusion. In contrast, in the placebo group, atheroma volume increased by 0.14 percent.

While the numbers are small, researchers said that no treatment to date has been associated with regression of plaque in such a short amount of time. Stay tuned.

Citation: *Journal of the American Medical Association*, Nov. 5, 2003.

10. How to use a new blood test to measure heart attack risk. For the first time, a panel of experts convened by the American Heart Association and the Centers for Disease Control and Prevention recommended in 2003 limited use of a new blood test for assessing heart disease risk. The test measures C-reactive protein, or CRP, a marker of inflammation. Several studies have demonstrated that increased concentrations of CRP appear to be associated with increased risk for coronary heart disease, sudden death and peripheral arterial disease.

The writing group emphasized that the new test – known as highly sensitive C-reactive protein (hs-CRP) test – does not fit in the same

category as cholesterol testing or high blood pressure screening currently recommended. They said the test might be useful when a physician is undecided about a course of treatment for a patient who is considered intermediate risk.

Citation: Print issue of *Circulation: Journal of the American Heart Association*. January 28, 2003.

AHA News
12/31/2001

American Heart Association's top 10 research advances for 2001

2001 Year-end Report

DALLAS, Dec. 31 - New treatments for heart failure - implantable heart devices and cell-grown tissues - are among the top 10 research advances in heart disease and stroke for 2001, says David Faxon, M.D., president of the American Heart Association.
Other major milestones include drug-eluting stents and the use of stem cell transplants to repair stroke-damaged brains.
Created in 1996, the "Top 10" list highlights major gains in heart disease and stroke research.

1. Drug-eluting stents to prevent reblockage of coronary arteries. In what could become one of the biggest breakthroughs in treating cardiovascular disease, scientists used drug-coated stents to prevent the reblockage of the stented section of a coronary artery. Reblockage occurs in about 15 percent to 30 percent of angioplasty patients who receive stents. Researchers involved in several clinical trials have found that stents coated with a drug prevent the overgrowth of cells that typically causes the stented artery to reblock.

The RAVEL study of 238 patients at 19 centers across Europe and Latin America compared patients who received a standard stent to those who received one coated with Sirolimus, an antibiotic that inhibits the overgrowth of cells. The results were presented at September's European Society of Cardiology meeting in Stockholm. No patients who received the drug-eluting stent had restenosis (reblockage) at the seven-month follow-up, but 26 percent of those who received conventional stents had reblockage. Patients who received the drug-eluting stent also had a significant reduction in major cardiac events such as heart attack or death during the follow-up period (3.3 percent vs. 27.1 percent).

Results from ELUTES (European Evaluation of Paclitaxel Eluting Stent) were presented at the American Heart Association's 2001 Scientific Sessions in Anaheim, Calif., in November. The 192 patients in ELUTES were divided into five groups. Four groups received a stent coated with varying doses of the cancer drug. Patients in the fifth group were used as controls. At six-months follow-up, the group that received the stent with the highest dose had a 3.1 percent restenosis rate compared with a 20.6 percent reblockage rate in the control group. A number of other drug-eluting stent trials are under way.

2. Implantable left ventricular assist devices serve as "replacement therapy" for end-stage heart failure. Heart failure patients treated with a left ventricular assist device (LVAD) lived longer and better than patients who did not receive the device. In a study called REMATCH, 68 patients

received the LVAD and 61 patients were treated with drugs and medical monitoring.

Surgeons implanted the pump, which is the size of a compact disc player, into the upper part of the abdominal wall or in the peritoneal lining. A tube on the device enters the left ventricle and drains blood from the ventricle into the device. The pump sends the blood to the aorta. Another tube attached to the pump extends outside the body and is attached to a videotape-sized battery pack, which is worn on a shoulder holster. Patients wear a beeper-sized control system on a belt.

The device assists the heart's left ventricle, which becomes weakened in heart failure. The LVAD lets blood pass from the left ventricle to the aorta, which supplies oxygen-rich blood to the brain and the rest of the body.

In early human trials, researchers tested the LVAD as a "bridge-to-transplant device." This paved the way for its ultimate use - a long-term heart replacement therapy for patients not eligible for heart transplants. An estimated 50,000 to 100,000 people with end-stage heart failure could benefit from this type of therapy.

3. Implantable heart showing promise. On July 2, 2001, 59-year-old Robert Tools became the first person to receive the AbioCor implantable heart. He lived for 151 days. Cause of death was severe abdominal bleeding according to his physician Robert D. Dowling, M.D., of Jewish Hospital in Louisville, Ky., who performed the procedure. Jewish Hospital is one of five sites participating in the AbioCor artificial heart clinical trial.

Tools, like other patients in the trial, had severe heart failure and was too ill for a heart transplant. The trial determined whether the implantable heart can extend life with acceptable quality for patients with less than 30 days' life expectancy, and for whom no other therapeutic alternative exists. To be accepted, patients must have severe heart failure affecting both the left and right ventricles of the heart and have a life expectancy of no more than 30 days.

The heart is implanted in the chest and mimics the function of the human heart by circulating blood through the body. It is battery-operated and weighs only about 2 pounds.

The heart may eventually be an alternative for patients who are candidates for heart transplants but for whom no donor human heart is available. An estimated 4.7 million Americans have congestive heart failure. Many of them would be candidates for a heart transplant, but only about 2,000 donor hearts are available each year in the United States.

4. Tissue engineering with bone marrow and cord blood grows heart parts. Cardiovascular surgery requires replacement parts such as heart valves, blood vessels and vascular patches, but their function may be complicated by blood clots, tissue overgrowth, limited durability, infection and the inability to grow. The body can reject donor tissue. Tissue engineering using a patient's own blood or cells offers an alternative source. It holds particular promise in pediatric surgery where a graft with growth potential is important.

Researchers at the University Hospital Zurich in Switzerland used human

bone marrow cells as a new cell type to engineer heart valves in the laboratory. The cells were seeded on heart valve scaffolds made from bioabsorbable materials and grown in a pulse duplicator bioreactor system that mimics the blood circulation of humans.

Heart valves open and close to let blood flow in only one direction as it is pumped through the heart's chambers. Each valve has several flap-like structures, called leaflets or cusps.

The engineered human valves opened and closed synchronously in the pulse duplicator system. Microscopic examination showed an even cell growth and mechanical function was comparable to natural human heart valves.

In 1999, this group was the first to grow a complete heart valve in the laboratory in a study that used cells from sheep blood vessel walls. The valves showed excellent functional performance in blood circulation and strongly resembled natural heart valves.

Another group used early-stage endothelial cells, called endothelial progenitor cells (EPCs), from human umbilical cord blood to create endothelial layers for cardiovascular tissue engineering. EPCs came from cord blood obtained after a C-section and were culture-grown.

The new cells were seeded onto a bioabsorbable polymer scaffold to make tissue strips with the potential to be molded into any form (valve, vessel, patch, etc.). The cells were treated with vascular endothelial growth factor (VEGF) and fibroblast growth factor (bFGF) to stimulate cell growth. The treated cells were grown in a pulse duplicator system for two weeks. The cells formed capillary-like tubes, indicating the start of blood vessel formation.

The researchers concluded that human umbilical cord blood is a valuable source of EPCs, providing novel cells for tissue engineering.

The exciting possibilities for this cell source include "banking" the cells for future use. Cord blood cells could potentially be used to create a tissue-engineered structure needed to correct a cardiac birth defect diagnosed prenatally. The new tissue could be ready to use when the baby is born - or even before birth for potential prenatal/fetal surgical repair.

In other cell transplant experiments, adult human cardiac myocytes (heart muscle cells) regenerated after heart attack. This means the heart may be able to replace damaged tissue by producing new functional cells. A subpopulation of myocytes that is not "terminally differentiated" re-entered the cell cycle and divided after the infarction. In similar research, adult stem cells derived from bone marrow regenerated, forming new functional heart cells when injected around the site of the heart attack.

5. Gene therapy shown to reduce angina. Experimental treatments using genes for vascular endothelial growth factor (VEGF) are not new. But in 2001 researchers brought a new twist to this pioneering treatment for coronary artery disease.

For the first time, researchers have data from a randomized, blinded, placebo-controlled trial indicating that blood flow to the heart improves

after VEGF2 treatment. Patients treated with the VEGF2 gene had less angina, increased their ability to exercise and had improved myocardial perfusion. Placebo treated patients had none of these changes.

VEGF is a naturally occurring protein that stimulates the proliferation and migration of endothelial cells and endothelial progenitor cells, leading to formation of new blood vessels. The theory is that injecting the gene into the heart triggers the growth of new blood vessels in the oxygen-starved heart muscle.

Previous trials suggested that gene transfer of VEGF diminished chest pain and increased blood flow to the heart. However, those studies used a surgical approach to directly inject the gene into the heart. Thus, it wasn't possible to have a placebo-controlled trial, a major limitation of the trials.

In the study, 19 patients with class III or IV angina - the most severe chest pain associated with heart disease - received six injections in their left ventricle of either a placebo solution (saline) or a VEGF2 gene therapy solution. The injections were made using a special catheter that can identify areas of the heart muscle that lack an adequate blood supply. The patients all tolerated the gene delivery procedure without complications.

Angina improved by two to three classes in eight of 12 patients who received the VEGF2 gene. One person reported that VEGF2 gene therapy completely eliminated chest pain. None of the six placebo patients experienced a significant reduction in angina class. The difference in outcome between the VEGF2- and placebo-treated patients was statistically significant, a surprising fact in this relatively small pilot study. A large, randomized trial is being planned.

6. Cholesterol-lowering drugs bring benefits to high-risk populations, even when LDL is normal. The MRC/BHF Heart Protection Study (HPS) is the world's largest randomized trial of cholesterol-lowering drugs and of antioxidant vitamins in people at increased risk of coronary heart disease (CHD). Even though they have been used for decades, statin drugs' usefulness in particular populations is unknown. The study is one of the first to include substantial numbers of people in categories that were excluded from other studies of this kind.

Patients aged 40-80 with a history of occlusive vascular disease or diabetes were eligible, provided their doctors did not consider statin therapy a clear choice. Between July 1994 and May 1997, 20,536 patients were recruited in 69 United Kingdom hospitals. Previous heart attack was reported by 8,510 (most of whom were elderly, female or had "low" total cholesterol levels). They also had other forms of cardiovascular disease such as previous stroke or TIA, peripheral artery disease, diabetes (with overlap between these categories).

Participants were randomly allocated 40 mg of simvastatin daily or matching placebo for 5 ½ years. Vitamins were given to half of each treatment group (600 mg vitamin E, 250 mg vitamin C, 20 mg beta-carotene daily). The other half received a placebo. The vitamins had no effect on vascular or related death or disease.

Cholesterol-lowering therapy reduced total and vascular mortality, total CHD, stroke, and revascularization procedures. After making allowance for non-compliance (including non-study statin use), simvastatin given at 40

mg daily reduced "major vascular events" by at least one-third among patients (women, people over 70 years old, those with LDL below 3.0 mmol/l [116 mg/dL] and those with diabetes or non-coronary occlusive disease without pre-existing CHD).

Further development in treating lipid disorders came from recommendations from the National Cholesterol Education Panel (NCEP). They suggest a new approach to treat adults with elevated blood cholesterol. The recommendations, the NCEP Adult Treatment Panel III (ATP III), call for physicians to use "the basic principle" to match the intensity of the therapy to the person's risk. A table that estimates a person's 10-year risk is used as a guide for treatment goals. Risk is calculated by adding points based on the presence of risk factors such as elevated cholesterol, smoking status, blood pressure, HDL and age. Individuals with two or more risk factors should be treated more intensely.

Other new features of ATP III focus on treating diabetes, multiple metabolic syndrome and other risks factors. The panel supports a complete lipoprotein profile: total, LDL and HDL cholesterol and triglyercerides, rather than screening for total cholesterol or HDL alone. It presents strategies for promoting lifestyle changes to reduce risk and drug therapies. The report recommends new targets for optimal LDL levels. Optimal levels of LDL are 100 mg/dL or less; and low HDL optimal levels should be from 35 to 40 mg/dL. The triglycerides classification cut point has been lowered.

Primary prevention of cardiovascular disease should begin with reducing intakes of saturated fat, increased physical activity and weight control. Secondary prevention should include reducing LDL cholesterol below 100 mg/dL by lifestyle changes and drug therapy.

7. New genetic predictors of cardiovascular disease. In one of the largest genetic studies of its kind, researchers discovered three genetic variants that may explain why some families are prone to premature heart disease. Investigators at 15 institutions used "high throughput" microarray genotyping to sift through 62 genes of 352 people with coronary artery disease and 418 individuals without. The culprit genes regulate thrombospondins (TSP), a family of matrix proteins that helps blood clot and repair arteries.

The investigators discovered distinctive variations in the genes of families with coronary artery disease, including a protective one. Changes known as single-nucleotide polymorphisms (SNP) were observed in genes that encode the different thrombospondin proteins. These proteins govern new blood vessel growth, blood clotting and the blood vessel response to oxidized low-density lipoprotein cholesterol (LDL).

In the families with coronary artery disease, at least two members had a heart attack or coronary revascularization at a young age - before age 45 in men and age 50 in women. The variant identified as thrombospondin-1 (TSP-1) was associated with a nine-fold risk of premature heart attack. Those with the TSP-4 variant had an 89 percent greater risk of heart attack. The TSP-2 variant was linked to a 69 percent lower heart attack risk.

Individuals with two copies of one of the variants, called the missense